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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| <p>(21) International Application Number: PCT/US93/01105</p> <p>(22) International Filing Date: 4 February 1993 (04.02.93)</p> <p>(30) Priority data: 07/845,885 4 March 1992 (04.03.92) US</p> <p>(71) Applicant: ABBOTT LABORATORIES [US/US]; CHAD 0377/AP6D-2, One Abbott Park Road, Abbott Park, IL 60064-3500 (US).</p> <p>(72) Inventors: ZYDOWSKY, Thomas, M. ; 2630 Delany Road, Waukegan, IL 60087 (US). DE, Biswanath ; 2823 Whispering Oaks Drive, Buffalo Grove, IL 60089 (US). SHIOSAKI, Kazumi ; 1021 Mayfair, Libertyville, IL 60048 (US). BASHA, Fatima, Z. ; 41 East Heron Drive, Lake Forest, IL 60045 (US). WINN, Martin ; 1263 Carlisle Place, Deerfield, IL 60015 (US). DeBERNARDIS, John, F. ; 2500 Colony Avenue, Lindenhurst, IL 60046 (US). VON GELDERN, Thomas, W. ; 4209 W. Solon Road, Richmond, IL 60071 (US). YAMAMOTO, Diane, M. ; 36143 N. Grand Oaks, Gurnee, IL 60031 (US). ROSENBERG, Saul, H. ; 1110 Fairlawn Drive, Libertyville, IL 60048 (US). KERKMAN, Daniel, J. ; 21 Cremin Drive, Lake Villa, IL 60046 (US). BOYD, Steven, A. ; 410 Lakeview, Mundelein, IL 60060 (US). FUNG, Anthony, K, L. ; 1145 Magnolia Avenue, Gurnee, IL 60031 (US).</p> | | <p>(74) Agents: GORMAN, Edward, H., Jr. et al.; Abbott Laboratories, CHAD 0377/AP6D-2, One Abbott Park Road, Abbott Park, IL 60064-3500 (US).</p> <p>(81) Designated States: European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>With international search report.</i></p> |
| <p>(54) Title: ANGIOTENSIN II RECEPTOR ANTAGONISTS</p> <p>(57) Abstract</p> <p>Compounds are disclosed having formula (I). The compounds of the invention are angiotensin II receptor antagonists.</p> <div style="text-align: center;"> <p>(I)</p> </div> | | |

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ANGIOTENSIN II RECEPTOR ANTAGONISTS

Technical Field

This invention relates to compounds and compositions which block angiotensin II receptors, processes for making such compounds, synthetic intermediates employed in these processes and a method of treating hypertension, edema, renal failure, benign prostatic hypertrophy, diabetic nephropathy, Alzheimer's disease or congestive heart failure with such compounds. The present invention also relates to compositions and a method for treating glaucoma, preventing or treating atherosclerosis, preventing or treating stroke and treatment of a variety of obesity-related disorders with such compounds. The present invention also relates to compositions and a method for treating CNS disorders.

Background of the Invention

Blood pressure is regulated by a multitude of interrelated factors involving neural, vascular and volume-related effects. The renin-angiotensin system (RAS) is one of the important blood pressure regulating systems.

The RAS functions as shown in the scheme below. Low renal perfusion pressure stimulates the juxtaglomerular cells of the kidney to produce

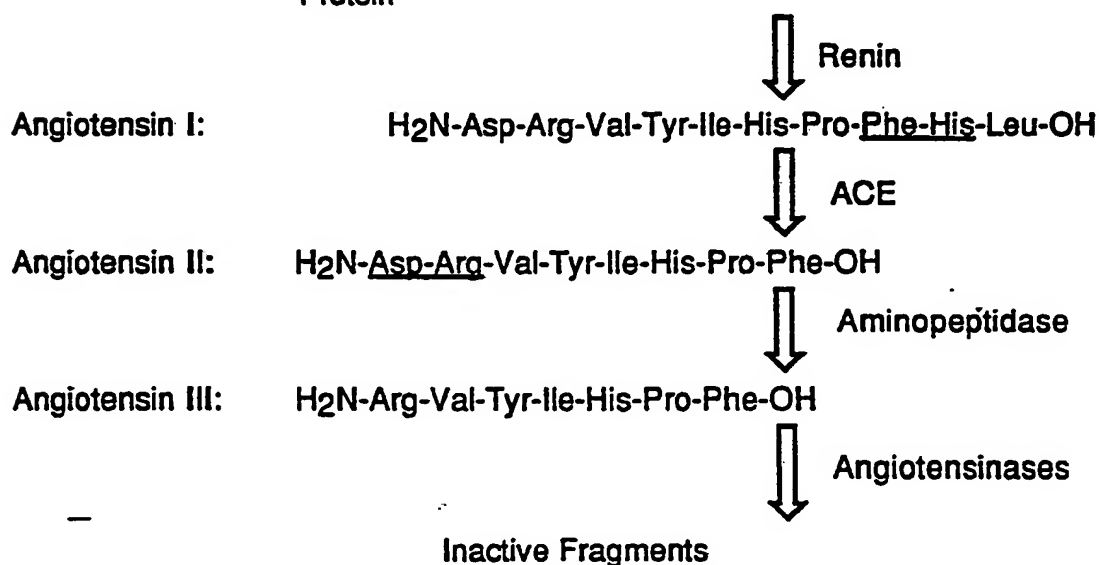
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the proteolytic enzyme renin. This enzyme acts on a circulating protein, angiotensinogen, cleaving off a decapeptide angiotensin I. Angiotensin I is then cleaved to the octapeptide angiotensin II by angiotensin converting enzyme (ACE). Angiotensin II is the most powerful pressor substance in the RAS. Angiotensin II binds to vascular smooth muscle receptors and induces vasoconstriction, but has little or no stimulating action on the heart.

Renin-Angiotensin System

Human

Angiotensinogen: H₂N-Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-His-Protein



Inhibitors of renin (for example enalkiren) and inhibitors of ACE (for example, captopril and enalapril) have clinical efficacy in treating hypertension and congestive heart failure. ACE inhibitors, however, have reported side effects including cough and skin rash.

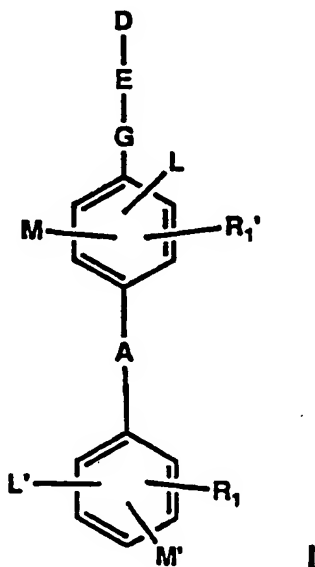
Peptidyl and non-peptidyl angiotensin II receptor antagonists are known. The peptidyl compound saralasin or [Sar¹,Ala⁸] angiotensin II has been found

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to be a potent antagonist of the actions of angiotensin II. Saralasin, however, has several disadvantages. Because it is a peptide, saralasin has very poor oral bioavailability. The use of saralasin, therefore, is limited to administration to hospitalized patients by continuous intravenous infusion. Saralasin is also known to cause an initial increase in blood pressure after intravenous administration due to its activity as an angiotensin receptor agonist. Therefore, non-peptidyl angiotensin II receptor antagonists are preferred.

Disclosure of the Invention

In accordance with the present invention, there are compounds of the formula I:



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wherein

A is

- (i) a covalent bond,
- (ii) -O-,
- (iii) -C(O)-,
- (iv) -CH₂-,
- (v) -S-, -S(O)- or -S(O)₂-;

E-G is

- (i) -N(R₅)-,
- (ii) -O-,
- (iii) -S-,
- (iv) -N(R₅)-CH(R₅)-,
- (v) -O-CH(R₅)-,
- (vi) -S-CH(R₅)-,
- (vii) -C(R₅')-CH(R₅)-,
- (viii) -CH(R₅)-C(R₅')-(R₅)-,
- (ix) -CH(R₅)-N(R₅)-,
- (x) -CH(R₅)-O-,
- (xi) -CH(R₅)-S-,
- (xii) -N(R₅)-N(R₅)-,
- (xiii) -C(R₅)=C(R₅)- or
- (xiv) -CH(R₅)-C(R₅')-(R₅)-N(R₅)- wherein at each occurrence R₅ is independently selected from hydrogen, loweralkyl, alkoxy-substituted loweralkyl, halo-substituted loweralkyl, carboxy-substituted loweralkyl, heterocyclic-substituted loweralkyl, alkenyl, alkynyl, cycloalkyl or cycloalkylalkyl and R₅' is hydrogen, halo, hydroxy, carboxy, alkoxy or thioalkoxy;

L, L', M and M' are independently selected from

- (i) hydrogen,

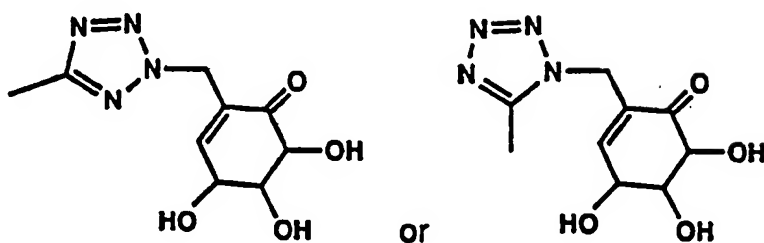
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- (ii) loweralkyl,
- (iii) halo-substituted loweralkyl,
- (iv) halo,
- (v) -CN,
- (vi) -NO₂,
- (vii) -OH,
- (viii) hydroxy-substituted loweralkyl,
- (ix) alkoxy-substituted loweralkyl,
- (x) -NH₂,
- (xi) alkylamino,
- (xii) dialkylamino,
- (xiii) -SH,
- (xiv) alkoxy and
- (xv) thioalkoxy;

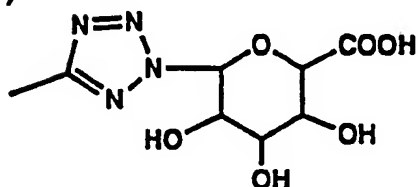
R₁ and R₁' are independently selected from

- (i) tetrazolyl,

(ii)



(iii)



- (iv) -NH-C(=N(R_{50a}))(R_{51a}) wherein R_{50a} is hydrogen, -CN or -NO₂ and

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R_{51a} is hydrogen, loweralkyl, alkylamino, dialkylamino, alkoxy or thioalkoxy,

- (v) -NH(R_{51b}) wherein R_{51b} is a 5-membered aromatic heterocyclic ring wherein the heterocyclic ring contains 1, 2, 3 or 4 nitrogen atoms or 1 nitrogen atom and 1 oxygen atom or 2 nitrogen atoms and 1 oxygen atom or 1 oxygen atom and 1 sulfur atom and wherein the 5-membered heterocyclic ring is unsubstituted or substituted with a substituent selected from amino, alkylamino, dialkylamino, hydroxy, alkoxy, thioalkoxy, halo, loweralkyl and halo-substituted loweralkyl,
- (vi) -COOR₆ or -CH₂COOR₆ wherein R₆ is hydrogen or a carboxy-protecting group or
- (vii) -NHS(O)₂R₇ or -CH₂NHS(O)₂R₇ or -NHC(O)R_{7a} or -CH₂NHC(O)R_{7a} wherein R₇ is loweralkyl, halo-substituted loweralkyl or -NR_{7b}R_{7c} wherein R_{7b} and R_{7c} are independently selected from hydrogen and loweralkyl and R_{7a} is loweralkyl, halo-substituted loweralkyl, amino, alkylamino, dialkylamino or -COOH;
- (viii) -C(O)NR₅₀R₅₁ or -CH₂C(O)NR₅₀R₅₁ or -NHC(O)NR₅₀R₅₁ or -CH₂NHC(O)NR₅₀R₅₁ or -NHC(S)NR₅₀R₅₁ or -CH₂NHC(S)NR₅₀R₅₁ wherein R₅₀ and R₅₁ are independently selected from hydrogen, loweralkyl, hydroxy, alkoxy, hydroxy-substituted loweralkyl, alkoxy-substituted loweralkyl, alkoxy-substituted alkoxy and -S(O)₂R_{50a} wherein R_{50a} is loweralkyl or aryl, or R₅₀ and R₅₁ taken together with the nitrogen atom to which they are attached form a 5- to 7-membered aliphatic heterocycle;
- (ix) -CH₂OR₅₂ wherein R₅₂ is selected from hydrogen, loweralkyl and -C(O)R₅₃ wherein R₅₃ is hydrogen, loweralkyl or aryl;
- (x) -CH(OH)R_{52a} or -C(O)R_{52a} wherein R_{52a} is loweralkyl, halo-substituted loweralkyl, -CF₂COOR_{53a} or -CH₂COOR_{53a} wherein R_{53a} is hydrogen or a carboxy-protecting group,
- (xii) -CH₂NR₅₄R₅₅ wherein R₅₄ is selected from hydrogen, loweralkyl, -C(O)R₅₆, -C(O)NR₅₆R₅₇ and -S(O)₂R₅₈ wherein R₅₆ is selected from hydrogen, loweralkyl and aryl and R₅₈ is selected from lower

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alkyl and halo-substituted loweralkyl and wherein R_{55} and R_{57} are independently selected from hydrogen, loweralkyl, hydroxy and alkoxy;

(xiii) $-\text{SO}_3\text{H}$, $-\text{OSO}_3\text{H}$ or $-\text{CH}_2\text{SO}_3\text{H}$,

(xiv) $-\text{OPO}_3\text{H}_2$, $-\text{PO}_3\text{H}_2$ or $-\text{CH}_2\text{PO}_3\text{H}_2$,

(xv) $-\text{SO}_2\text{NR}_{50}\text{R}_{51}$ or $-\text{CH}_2\text{SO}_2\text{NR}_{50}\text{R}_{51}$ wherein R_{50} and R_{51} are defined as above and

(xvi) $-\text{C}(\text{O})\text{NHSO}_2\text{R}_{60}$, $-\text{C}(\text{O})\text{NHC}(\text{O})\text{R}_{60}$ or $-\text{C}(\text{O})\text{NHNHSO}_2\text{R}_{60}$ wherein R_{60} is loweralkyl, halo-substituted loweralkyl or aryl;

with the proviso that one of R_1 and R_1' is hydrogen, but R_1 and R_1' are not both hydrogen;
and

D is

(i) a bicyclic heterocycle comprising a 6-membered ring fused to a 5-membered ring, the bicyclic heterocycle comprising at least one heteroatom selected from N, O and S; the 6-membered ring of the bicyclic heterocycle comprising 0, 1, 2 or 3 nitrogen atoms or 1 nitrogen atom and 1 oxygen atom or 1 nitrogen atom and 1 sulfur atom or 1 oxygen atom and 1 sulfur atom or 2 oxygen atoms or 2 sulfur atoms or 1 oxygen atom or 1 sulfur atom, the remaining ring atoms being carbon atoms and the 6-membered ring comprising 0, 1, 2 or 3 double bonds; the 5-membered ring of the bicyclic heterocycle comprising 0, 1, 2 or 3 nitrogen atoms or 1 nitrogen and 1 oxygen atom or 1 nitrogen and 1 sulfur atom or 1 oxygen atom and 1 sulfur atom or 1 sulfur atom or 1 oxygen atom, the remaining ring atoms being carbon atoms and the 5-membered ring comprising 0, 1 or 2 double bonds; the nitrogen atoms of the bicyclic heterocycle can be substituted with a substituent R_2 wherein at each occurrence R_2 is independently selected from hydrogen, loweralkyl, carboxy-substituted loweralkyl or alkoxycarbonyl-substituted loweralkyl; the nitrogen atoms of the bicyclic heterocycle can be oxidized; one or two carbon atoms of the bicyclic heterocycle can be substituted with an oxo ($=\text{O}$) substituent and the sulfur atoms of the bicyclic

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heterocycle can be substituted with one or two oxo (=O) substituents; the bicyclic heterocycle can be substituted with one, two or three substituents independently selected from R_3 and R_4 , R_3 being bonded to a carbon atom or a nitrogen atom of the bicyclic heterocycle and R_4 being bonded to a carbon atom or a nitrogen atom of the bicyclic heterocycle, wherein

R_3 is

- (i) hydrogen,
- (ii) loweralkyl,
- (iii) halo,
- (iv) halo-substituted loweralkyl,
- (v) thioalkoxy,
- (vi) alkoxy-substituted loweralkyl,
- (vii) thioalkoxy-substituted loweralkyl,
- (viii) aryl,
- (ix) arylalkyl,
- (x) $-\text{NO}_2$,
- (xi) $-\text{COOR}_8$ wherein R_8 is hydrogen or a carboxy-protecting group,
- (xii) $-\text{OR}_9$ wherein R_9 is hydrogen, loweralkyl, halo-substituted loweralkyl, aryl, arylalkyl, heterocyclic-substituted loweralkyl or $-\text{C(O)}\text{R}_{10}$ wherein R_{10} is loweralkyl, halo-substituted loweralkyl, $-\text{PO}_3\text{H}_2$ or $-\text{NR}_{11}\text{R}_{12}$ wherein R_{11} and R_{12} are independently selected from hydrogen and loweralkyl and
- (xiii) $-\text{NR}_{13}\text{R}_{14}$ or $-\text{CH}_2\text{NR}_{13}\text{R}_{14}$ wherein R_{13} and R_{14} are independently selected from (1) hydrogen, (2) lower alkyl, (3) arylalkyl, (4) $-\text{C(O)}\text{R}_{15}$, (5) $-\text{S(O)}_2\text{R}_{15}$ wherein R_{15} is loweralkyl or halo-substituted loweralkyl and (6) $-\text{R}_{16}\text{-R}_{17}$ wherein R_{16} is alkylene and R_{17} is
 - (a) $-\text{NR}_{18}\text{R}_{19}$ wherein R_{18} and R_{19} are independently selected from hydrogen and loweralkyl or
 - (b) unsubstituted or loweralkyl substituted aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl,

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morpholinyl, thiomorpholinyl, pyridinyl or pyrimidinyl, or R₁₃ and R₁₄ taken together with the nitrogen atom to which they are attached form a 5- to 7-membered aliphatic heterocycle and

R₄ is

- (i) hydrogen,
- (ii) loweralkyl,
- (iii) halo-substituted loweralkyl,
- (iv) -CN,
- (v) -NO₂,
- (vi) -NH₂,
- (vii) -NH-C(=N(R_{25a}))(R_{26a}) wherein R_{25a} is hydrogen, -CN or -NO₂ and R_{26a} is hydrogen, loweralkyl, alkylamino, dialkylamino, alkoxy or thioalkoxy,
- (viii) -NH(R_{26b}) wherein R_{26b} is a 5-membered aromatic heterocyclic ring wherein the heterocyclic ring contains 1, 2, 3 or 4 nitrogen atoms or 1 nitrogen atom and 1 oxygen atom or 2 nitrogen atoms and 1 oxygen atom or 1 oxygen atom and 1 sulfur atom and wherein the 5-membered heterocyclic ring is unsubstituted or substituted with a substituent selected from amino, alkylamino, dialkylamino, hydroxy, alkoxy, thioalkoxy, halo, loweralkyl and halo-substituted loweralkyl,
- (ix) -CHO or -CH(=N-OH),
- (x) tetrazolyl,
- (xi) -NHS(O)₂R₂₀ or -CH₂NHS(O)₂R₂₀ or -NHC(O)R₂₁ or -N(OH)C(O)R₂₁ or -CH₂NHC(O)R₂₁ or -CH₂N(OH)C(O)R₂₁ wherein R₂₀ is loweralkyl, halo-substituted loweralkyl or -NR_{27a}R_{27b} wherein R_{27a} and R_{27b} are independently selected from hydrogen, -OH and loweralkyl and R₂₁ is loweralkyl, halo-substituted loweralkyl, amino, alkylamino, dialkylamino or -COOH,
- (xii) -CH(OH)R₂₂ or -C(O)R₂₂ wherein R₂₂ is loweralkyl, halo-substituted loweralkyl, -CF₂COOR₂₃ or -CH₂COOR₂₃

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wherein R₂₃ is hydrogen or a carboxy-protecting group,

(xiii) -COOR₂₄ or -CH₂COOR₂₄ wherein R₂₄ is hydrogen or a carboxy-protecting group,

(xiv) -C(O)NR₂₅R₂₆ or -CH₂C(O)NR₂₅R₂₆ or -NHC(O)NR₂₅R₂₆ or -CH₂NHC(O)NR₂₅R₂₆ or -NHC(S)NR₂₅R₂₆ or -CH₂NHC(S)NR₂₅R₂₆ wherein R₂₅ and R₂₆ are independently selected from hydrogen, loweralkyl, hydroxy, alkoxy, hydroxy-substituted loweralkyl, alkoxy-substituted loweralkyl, alkoxy-substituted alkoxy and -S(O)₂R_{28a} wherein R_{28a} is loweralkyl or aryl, or R₂₅ and R₂₆ taken together with the nitrogen atom to which they are attached form a 5- to 7- membered aliphatic heterocycle;

(xv) -CH₂OR₂₇ wherein R₂₇ is selected from hydrogen, loweralkyl and -C(O)R₂₈ wherein R₂₈ is hydrogen, loweralkyl or aryl;

(xvi) -CH₂NR₂₉R₃₀ wherein R₂₉ is selected from hydrogen, loweralkyl, -C(O)R₃₁, -C(O)NR₃₁R₃₂ and -S(O)₂R₃₃ wherein R₃₁ is selected from hydrogen, loweralkyl and aryl and R₃₃ is selected from loweralkyl and halo-substituted loweralkyl and wherein R₃₀ and R₃₂ are independently selected from hydrogen, loweralkyl, hydroxy and alkoxy;

(xvii) -SO₃H, -OSO₃H or -CH₂SO₃H,

— (xviii) -OPO₃H, -PO₃H₂ or -CH₂PO₃H₂,

(xix) -SO₂NR₂₅R₂₆ or -CH₂SO₂NR₂₅R₂₆ wherein R₂₅ and R₂₆ are defined as above and

(xx) -C(O)NHSO₂R₅₉, -C(O)NHC(O)R₅₉ or -C(O)NHNHSO₂R₅₉ wherein R₅₉ is loweralkyl, halo-substituted loweralkyl or aryl;

or D is

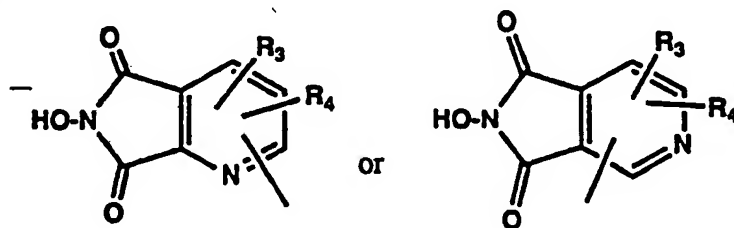
(ii) a bicyclic heterocycle comprising a 5-membered ring fused to a

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5-membered ring, the bicyclic heterocycle comprising at least one heteroatom selected from N, O and S; each of the 5-membered rings of the bicyclic heterocycle independently comprising 0, 1, 2 or 3 nitrogen atoms or 1 nitrogen and 1 oxygen atom or 1 nitrogen and 1 sulfur atom or 1 oxygen atom and 1 sulfur atom or 1 sulfur atom or 1 oxygen atom, the remaining ring atoms being carbon atoms and each of the 5-membered rings independently comprising 0, 1 or 2 double bonds; the nitrogen atoms of the bicyclic heterocycle can be substituted with a substituent R_2 wherein at each occurrence R_2 is independently selected from hydrogen, loweralkyl, carboxy-substituted loweralkyl or alkoxycarbonyl-substituted loweralkyl; the nitrogen atoms of the bicyclic heterocycle can be oxidized; one or two carbon atoms of the bicyclic heterocycle can be substituted with an oxo (=O) substituent and the sulfur atoms of the bicyclic heterocycle can be substituted with one or two oxo (=O) substituents; the bicyclic heterocycle can be substituted with one or two substituents independently selected from R_3 and R_4 , R_3 being bonded to a carbon atom or a nitrogen atom of the bicyclic heterocycle and R_4 being bonded to a carbon atom or a nitrogen atom of the bicyclic heterocycle, wherein R_3 and R_4 are defined as above;

or D is

(iii)



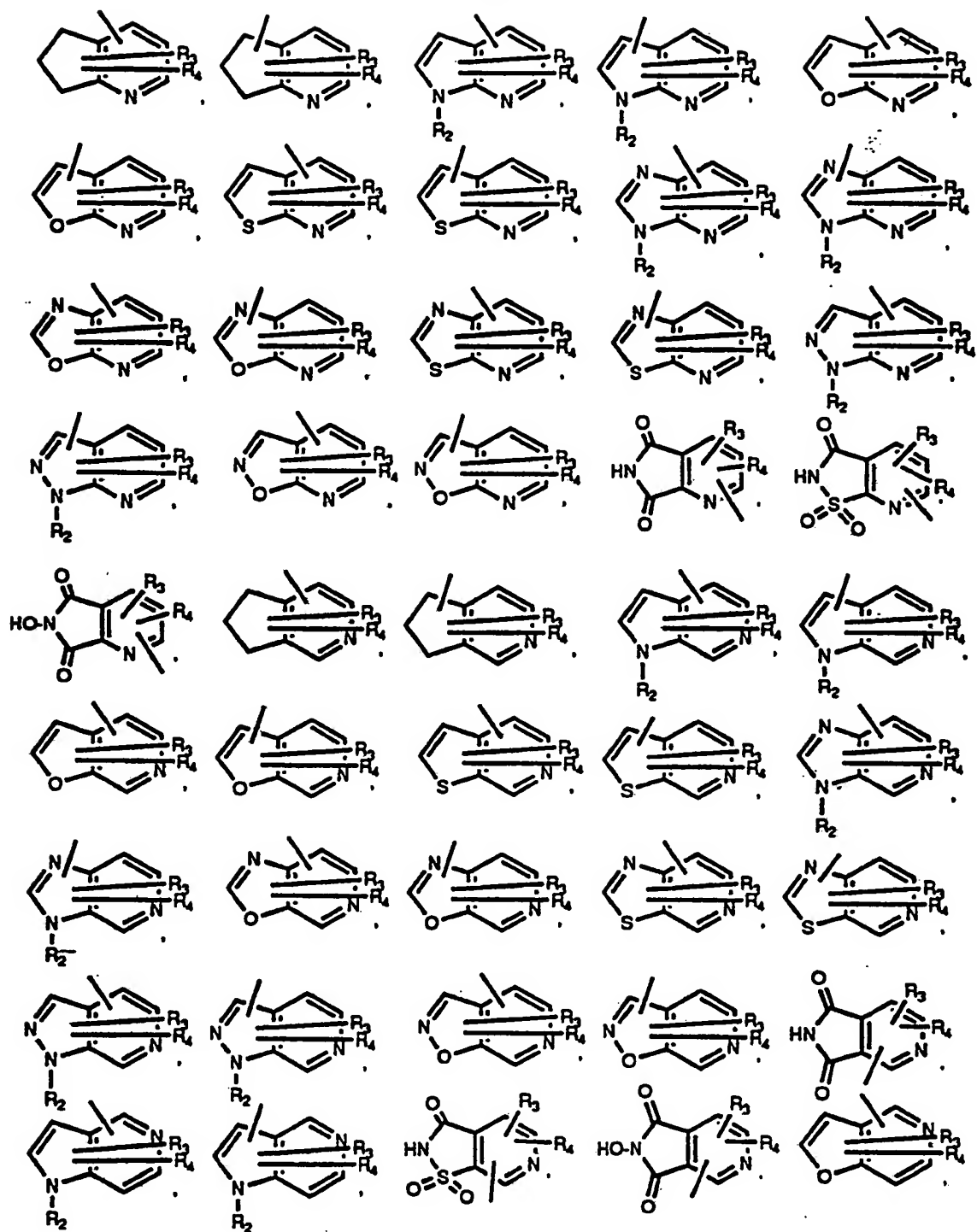
wherein R_3 and R_4 are defined as above;
or a pharmaceutically acceptable salt or prodrug thereof.

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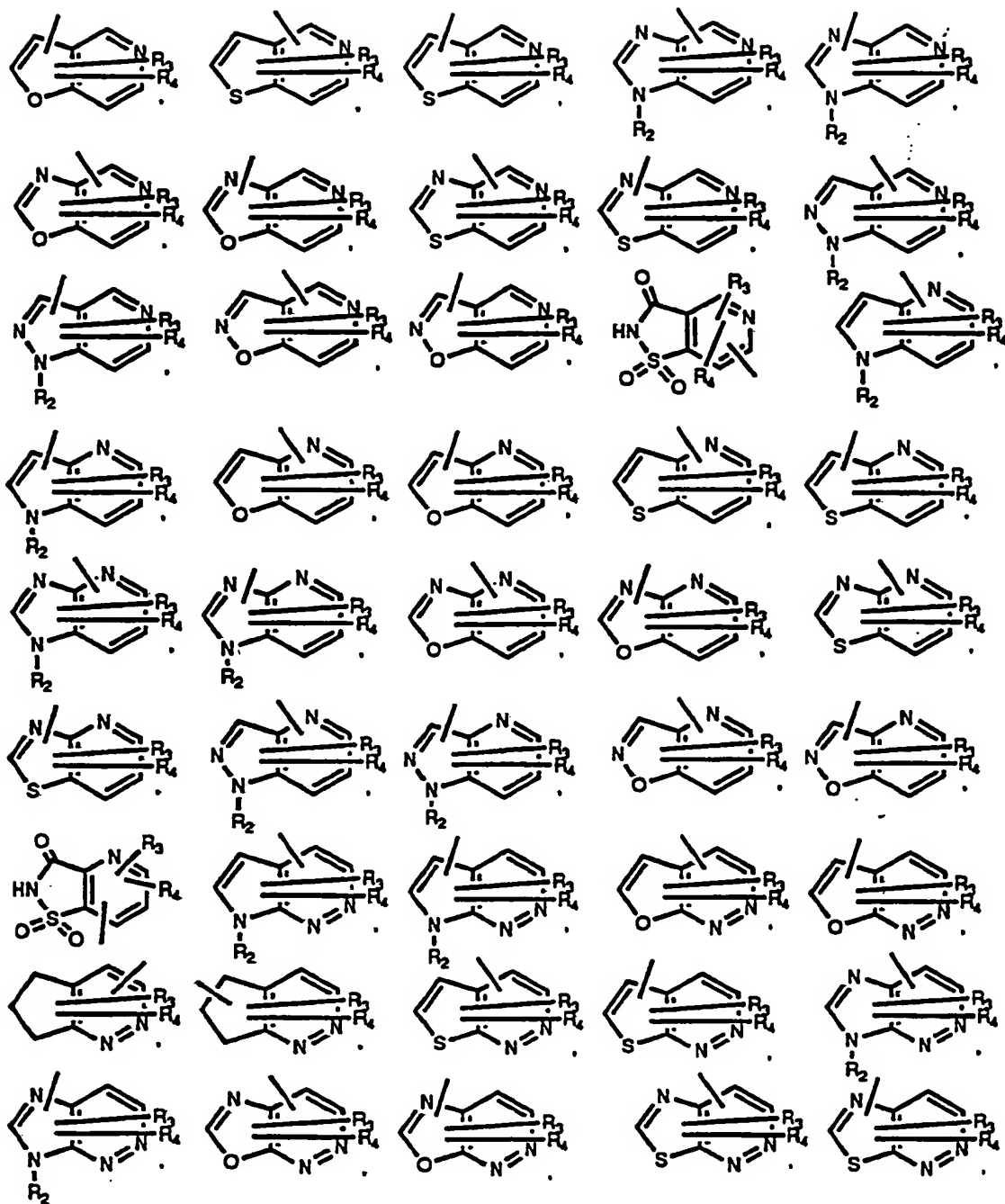
Preferred compounds of the invention are compounds wherein D is a substituted purinyl group, a substituted pyrazolopyrimidinyl group, a substituted triazolopyrimidinyl group, a substituted thiazolopyrimidinyl group, a substituted oxazolopyrimidinyl group, a substituted pyrrolopyrimidinyl group, a substituted thienopyrimidinyl group, a substituted furopyrimidinyl group, a substituted benzofuranyl group, a substituted isoxazolopyridinyl group or a substituted pyrrolopyridinyl group.

Representative bicyclic heterocycle substituents of the compounds of this invention are:

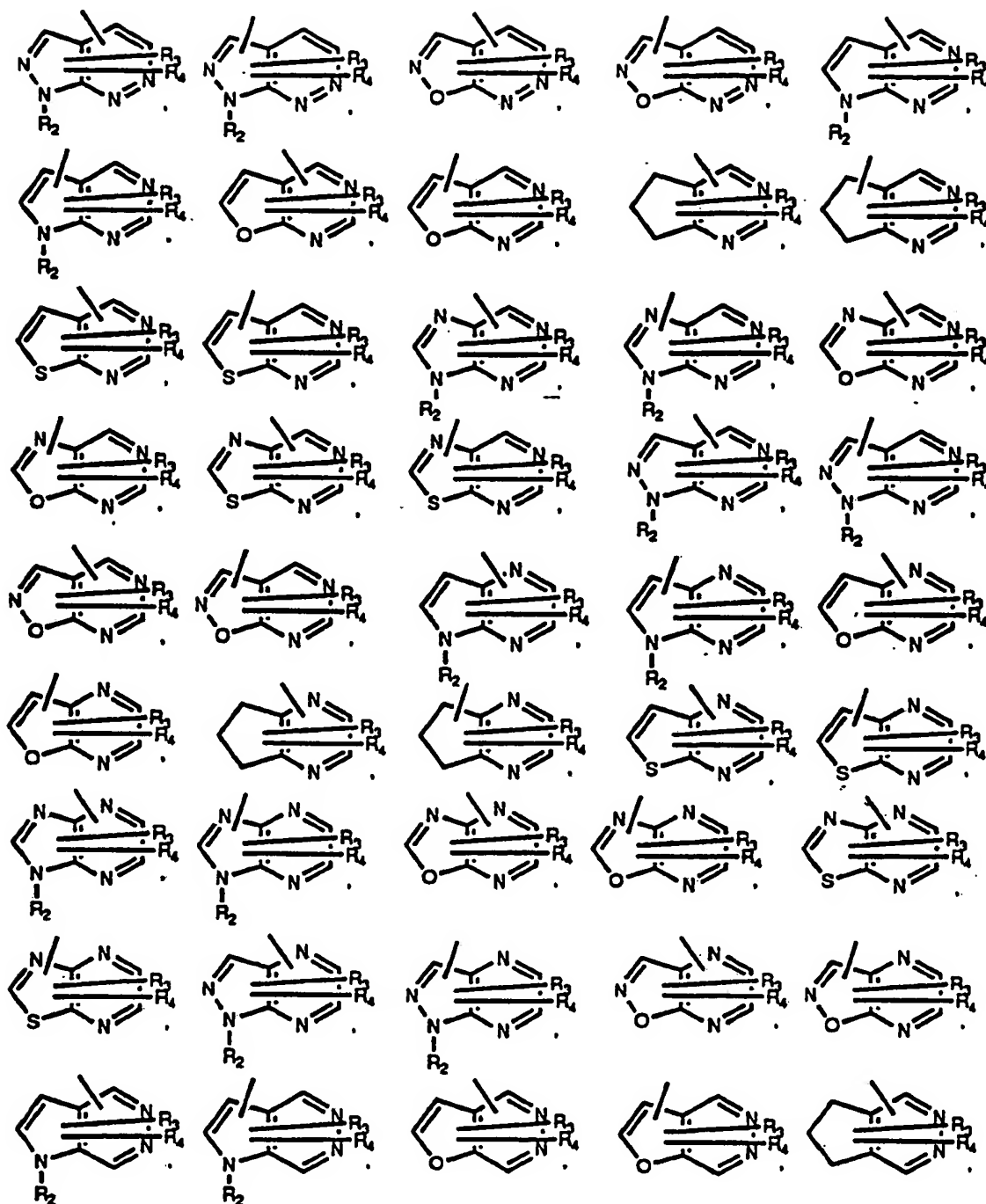
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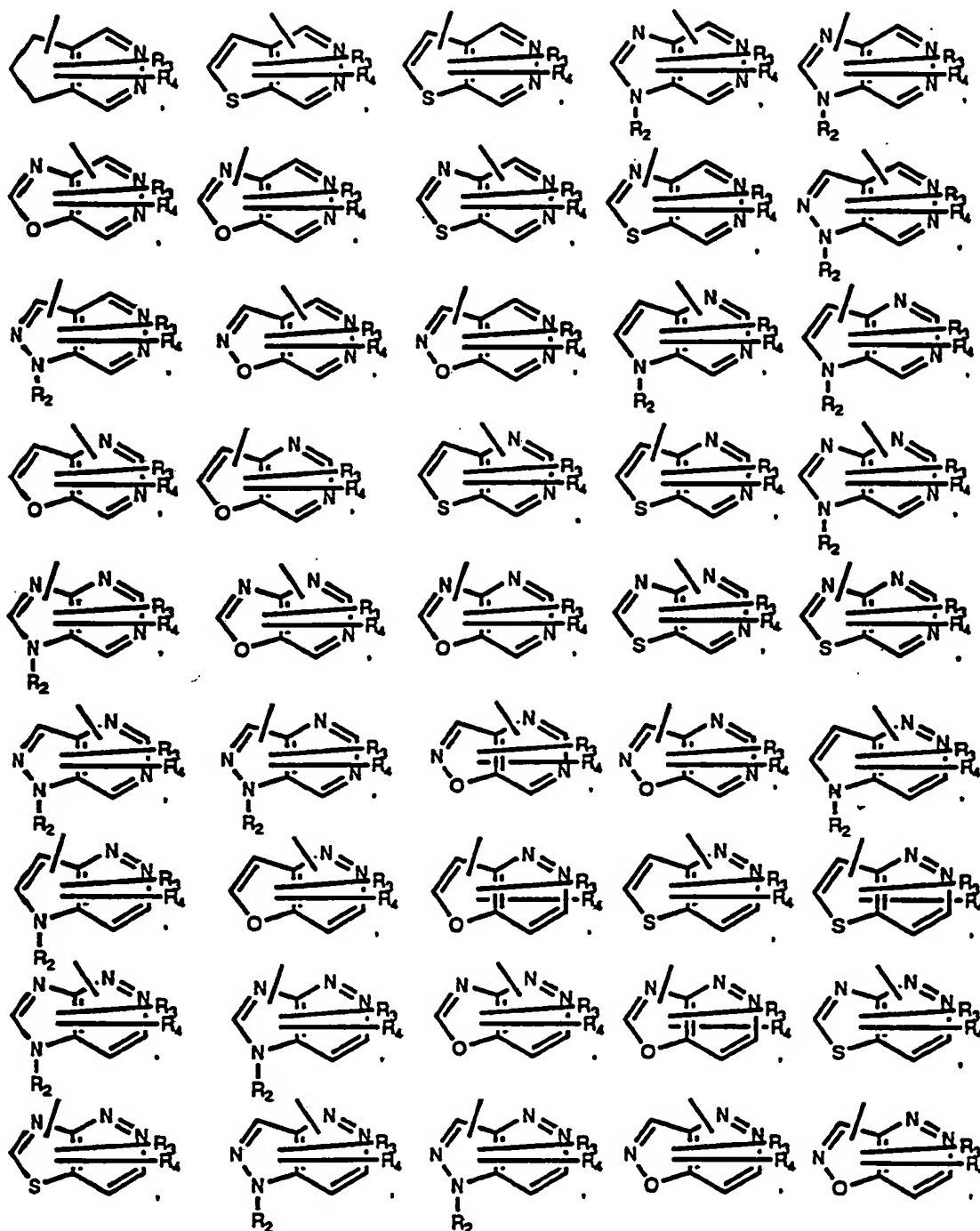
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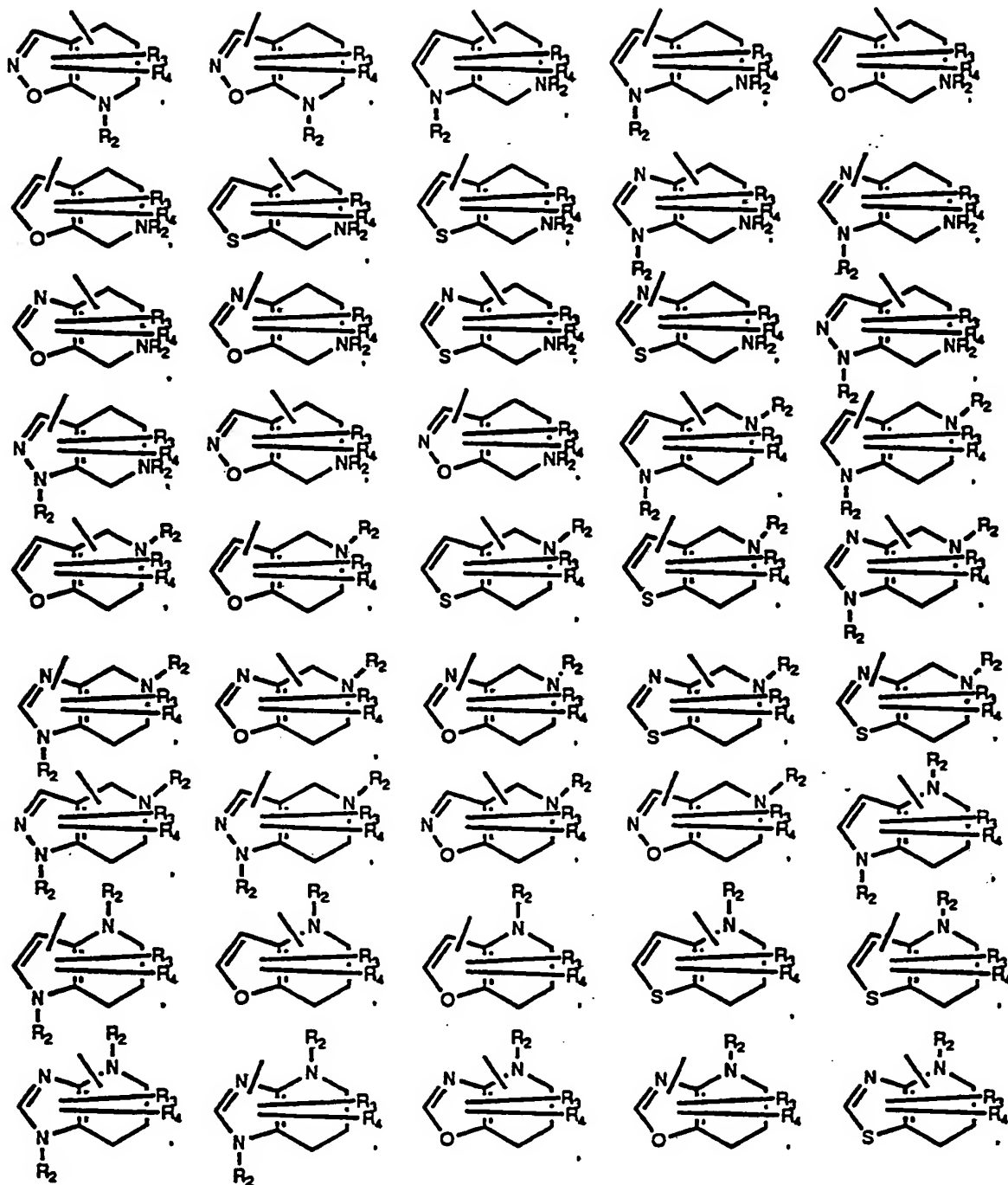
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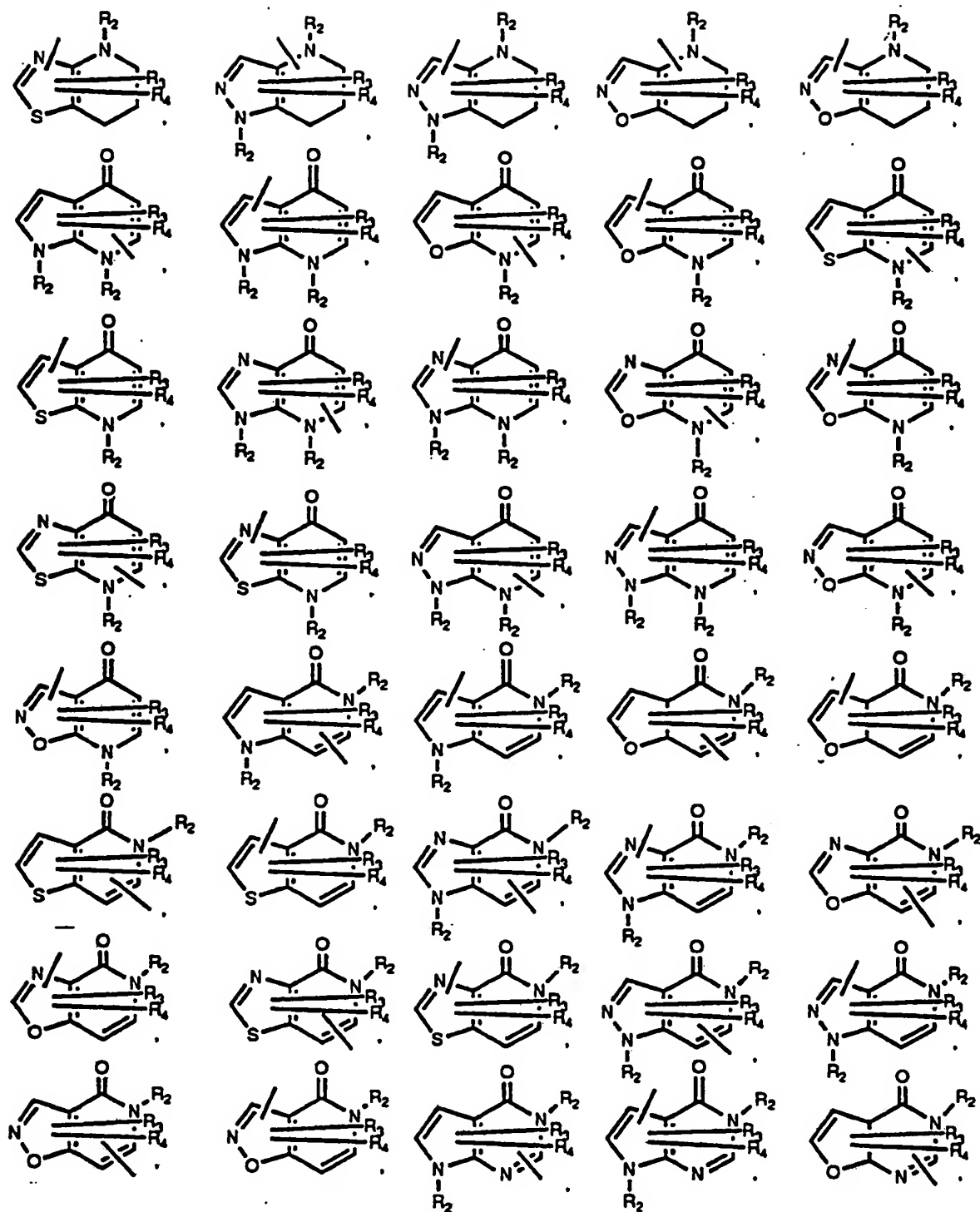
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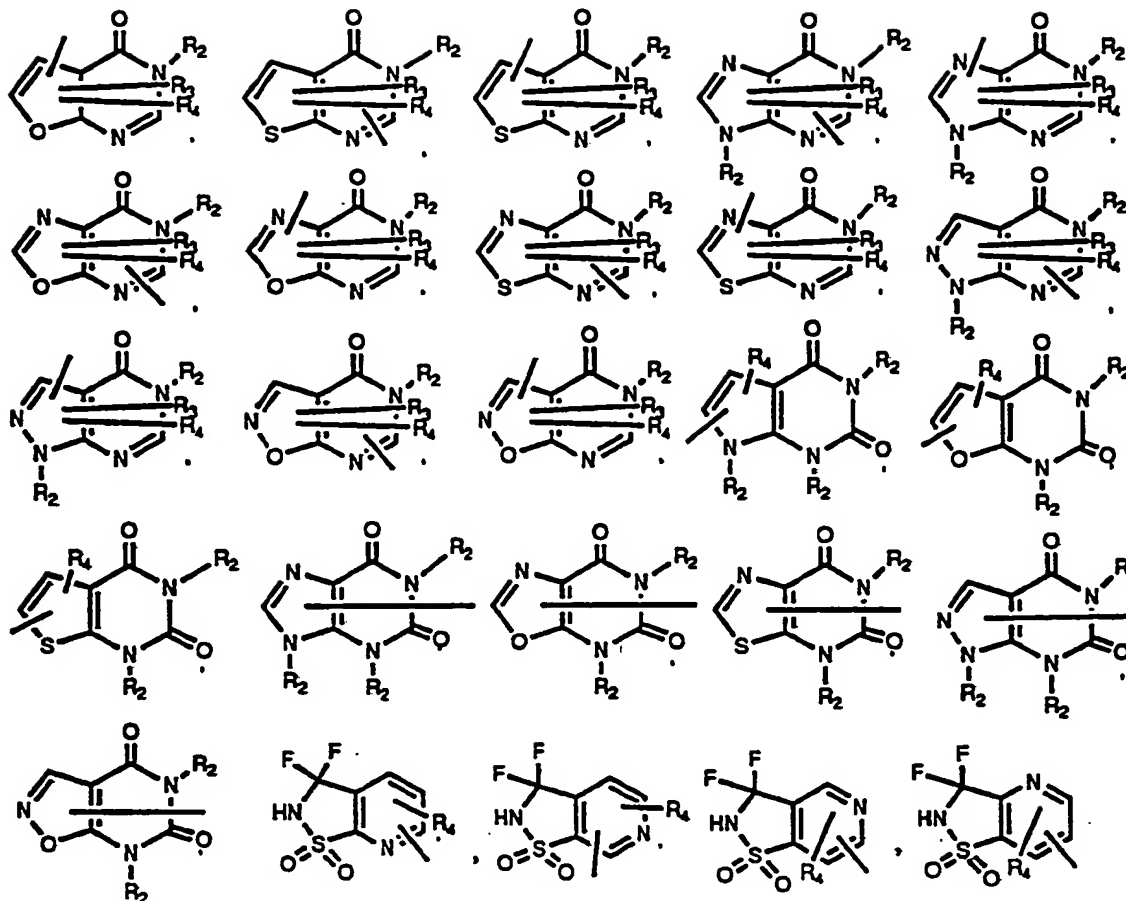
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and the like.

The term "loweralkyl" as used herein refers to branched or straight chain alkyl groups comprising one to ten carbon atoms, including methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, neopentyl and the like.

The term "alkenyl" as used herein refers to a branched or straight chain comprising two to ten carbon atoms which has one or more carbon-carbon double bonds, including vinyl, propenyl, butenyl and the like.

The term "alkynyl" as used herein refers to a branched or straight chain comprising two to ten carbon atoms which has one or more carbon-carbon triple bonds, including ethynyl, propynyl, butynyl and the like.

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The term "cycloalkyl" as used herein refers to an alicyclic group comprising from 3 to 7 carbon atoms, including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The term "cycloalkylalkyl" as used herein refers to a loweralkyl radical to which is appended a cycloalkyl group, including cyclopentylmethyl, cyclohexylmethyl and the like.

The term "alkylene" as used herein refers to a 1 to 10 carbon straight or branched chain di-radical, including $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2-$ and the like.

The term "halo-substituted loweralkyl" refers to a loweralkyl radical in which one or more of the hydrogen atoms are replaced by halogen, including chloromethyl, fluoroethyl, trifluoromethyl, pentafluoroethyl and the like.

The term "hydroxy-substituted loweralkyl" refers to a loweralkyl radical to which is appended one or two hydroxy ($-\text{OH}$) groups.

The term "halogen" or "halo" as used herein refers to I, Br, Cl or F.

The term "alkoxy" refers to $\text{R}_{34}\text{O}-$ wherein R_{34} is a loweralkyl or benzyl group. Representative examples of alkoxy groups include methoxy, ethoxy, t-butoxy, benzyloxy and the like.

The term "thioalkoxy" as used herein refers to $\text{R}_{35}\text{S}-$ wherein R_{35} is a loweralkyl or benzyl group.

The term "alkoxy-substituted loweralkyl" as used herein refers to a loweralkyl radical to which is appended an alkoxy group.

The term "thioalkoxy-substituted loweralkyl" as used herein refers to a loweralkyl radical to which is appended a thioalkoxy group. Representative thioalkoxy-substituted loweralkyl groups include methylthiomethyl, methylthioethyl, ethylthioethyl, propylthiomethyl and the like.

The term "hydroxy-substituted loweralkyl" as used herein refers to a loweralkyl radical to which is appended one or two hydroxy ($-\text{OH}$) groups.

The term "carboxy-substituted loweralkyl" as used herein refers to a loweralkyl radical to which is appended a carboxy group ($-\text{COOH}$), including carboxymethyl, carboxyethyl and the like.

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The term "alkoxycarbonyl" as used herein refers to $-C(O)OR_{36}$ wherein R_{36} is a carboxy-protecting group.

The term "alkoxycarbonyl-substituted loweralkyl" as used herein refers to a loweralkyl radical to which is appended an alkoxycarbonyl group.

The term "alkoxy-substituted alkoxy" as used here refers to an alkoxy radical to which is appended another alkoxy radical, including methoxymethoxy, methoxy ethoxy, ethoxyethoxy and the like.

The term "alkylamino" as used herein refers to $-NHR_{37}$ wherein R_{37} is a loweralkyl group.

The term "dialkylamino" as used herein refers to $-NR_{38}R_{39}$ wherein R_{38} and R_{39} are independently selected from loweralkyl.

The term "alkanoyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $-OC(O)R_{40}$ wherein R_{40} is loweralkyl.

The term "aroyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $-OC(O)R_{41}$ wherein R_{41} is aryl.

The term "alkoxycarbonylalkyl" as used herein refers to a loweralkyl radical to which is appended an alkoxycarbonyl group.

The term "alkoxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $-OC(O)OR_{42}$ wherein R_{42} is loweralkyl or cycloalkyl.

The term "alkoxycarbonylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended $-NHC(O)OR_{43}$ wherein R_{43} is loweralkyl.

The term "alkylaminocarbonylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended $-NHC(O)NHR_{44}$ wherein R_{44} is loweralkyl.

The term "alkanoylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended $-NHC(O)R_{45}$ wherein R_{45} is loweralkyl.

The term "heterocycliccarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $-OC(O)R_{46}$ wherein R_{46} is a heterocyclic group.

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The term "aryl" as used herein refers to a phenyl or a C₉ or C₁₀ bicyclic carbocyclic ring system having one or more aromatic rings, including naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like. Aryl groups can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, halo-substituted loweralkyl, alkoxy, thioalkoxy, alkoxycarbonyl, hydroxy, halo, mercapto, nitro, amino, alkylamino, dialkylamino, carboxaldehyde, carboxy and carboxamide.

The term "arylalkyl" as used herein refers to a loweralkyl radical to which is appended an aryl group. Representative arylalkyl groups include benzyl, phenylethyl, fluorobenzyl, fluorophenylethyl and the like.

The term "aliphatic heterocycle" as used herein refers to a saturated cyclic group containing 5 to 7 ring atoms and, in particular, at least 1 nitrogen atom in the ring and optionally 1 additional heteroatom selected from S, S(O)₂, O and N, with the remaining ring atoms being carbon atoms. The ring can be substituted on a carbon atom or a heteroatom, for example, with loweralkyl, alkoxy or alkoxy-substituted alkoxy. Representative aliphatic heterocycles include, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, S,S-dioxothiomorpholine, 4-methoxymethoxypiperidine and the like.

The term "heterocyclic group" or "heterocyclic" as used herein in the context of the terms "heterocyclic-substituted loweralkyl" and "5- to 7-membered aliphatic heterocycle" refers to any 3- or 4-membered ring containing a heteroatom selected from oxygen, nitrogen and sulfur, or a 5-, 6- or 7-membered ring containing one, two or three nitrogen atoms; one nitrogen and one sulfur atom; or one nitrogen and one oxygen atom; wherein the 5-membered ring has 0-2 double bonds and the 6- or 7-membered ring has 0-3 double bonds; wherein the nitrogen and sulfur heteroatoms can optionally be oxidized; wherein the nitrogen heteroatom can optionally be quaternized; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another 5-, 6- or 7-membered heterocyclic ring independently as defined above. Heterocyclics include indolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzofuryl, benzothienyl, azetidyl,

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pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, triazolyl, benzothienyl, homopiperazinyl, homopiperidinyl, homomorpholinyl and the like.

Heterocyclics can be unsubstituted or monosubstituted or disubstituted with substituents independently selected from hydroxy, halo, oxo (=O), amino, alkylamino, dialkylamino, alkoxy, thioalkoxy, carboxy, alkoxycarbonyl, loweralkyl, cycloalkyl, -OSO₃H and halo-substituted loweralkyl.

The term "heterocyclic-substituted loweralkyl" as used herein refers to a loweralkyl radical to which is appended a heterocyclic group.

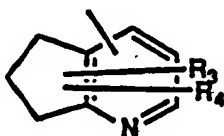
The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)), which is hereby incorporated by reference. N-protecting groups comprise carbamates, amides, N-alkyl derivatives, amino acetal derivatives, N-benzyl derivatives, imine derivatives, enamine derivatives and N-heteroatom derivatives. Preferred N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz) and the like.

— As used herein, the term "carboxy-protecting group" refers to a carboxy group which has been esterified with one of the commonly used carboxylic acid protecting ester groups employed to block or protect the carboxylic acid functionality while the reactions involving other functional sites of the compound are carried out. Carboxy-protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" pp. 152-186 (1981), which is incorporated herein by reference. In addition, a carboxy-protecting group can be used as a prodrug whereby the carboxy-protecting group can be readily cleaved *in vivo*, for example by enzymatic hydrolysis, to release the biologically active parent. T.

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Higuchi and V. Stella provide a thorough discussion of the prodrug concept in "Pro-drugs as Novel Delivery Systems", Vol 14 of the A.C.S. Symposium Series, American Chemical Society (1975). Such carboxy-protecting groups are well known to those skilled in the art, having been extensively used in the protection of carboxyl groups in the penicillin and cephalosporin fields, as described in U.S. Pat. No. 3,840,556 and 3,719,667, the disclosures of which are incorporated herein by reference. Examples of esters useful as prodrugs for compounds containing carboxyl groups can be found on pages 14-21 of "Bioreversible Carriers in Drug Design: Theory and Application", edited by E.B. Roche, Pergamon Press:New York (1987). Representative carboxy-protecting groups are C₁ to C₈ alkyl (e.g., methyl, ethyl or tertiary butyl and the like), benzyl and substituted derivatives thereof such as alkoxybenzyl or nitrobenzyl groups and the like, dialkylaminoalkyl (e.g., dimethylaminoethyl and the like), alkanoyloxyalkyl groups such as pivaloyloxymethyl or propionyloxymethyl and the like, aroyloxyalkyl, such as benzoyloxyethyl and the like, alkoxycarbonylalkyl, such as methoxycarbonylmethyl, cyclohexyloxycarbonylmethyl and the like, alkoxycarbonyloxyalkyl, such as t-butyloxycarbonyloxymethyl and the like, alkoxycarbonylaminoalkyl, such as t-butyloxycarbonylaminomethyl and the like, alkylaminocarbonylaminoalkyl, such as methylaminocarbonylaminomethyl and the like, alkanoylaminoalkyl, such as acetylaminomethyl and the like, heterocycliccarbonyloxyalkyl, such as 4-methylpiperazinylcarbonyloxymethyl and the like, dialkylaminocarbonylalkyl, such as dimethylaminocarbonylmethyl and the like, (5-(loweralkyl)-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-t-butyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like.

When used herein, a formula such as



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represents a bicyclic heterocycle where R₃ is bonded to either the 5-membered ring or the 6-membered ring and R₄ is bonded to either the 5-membered ring or the 6-membered ring.

When the compounds of formula I contain one asymmetric carbon atom, they can exist as pure enantiomers or mixtures of enantiomers. When the compounds of formula I contain more than one asymmetric carbon atom, they can exist as diastereomers, mixtures of diastereomers, diastereomeric racemates or mixtures of diastereomeric racemates. The present invention includes within its scope all of the isomeric forms. The terms "R" and "S" configuration used herein are as defined by IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem (1976) 45, 13-30.

In addition, in the compounds of the invention, combinations of substituents and/or variables (i.e., A, D, E, G, R₁, R₂, R₃, R₄, etc.) are permissible only if such combinations result in stable compounds.

In general, the compounds of this invention can be prepared by the processes illustrated in Schemes I through XVIII. It should be understood that substituents A, D, E, G, R₁, R₂, R₃, R₄, etc. as used herein correspond to the groups identified by formula (I). P is a protecting group. In the course of synthesis, certain groups present in the molecule, particularly carboxylic acid and tetrazole groups, are protected and deprotected as necessary. The term "protecting group" is well known in the art and refers to substituents on functional groups of compounds undergoing chemical transformation which prevent undesired reactions and degradations during a synthesis; see, for example, T.H. Greene, "Protective Groups in Organic Synthesis", John Wiley & Sons, New York (1981) for methods of introducing and removing appropriate protecting groups. Suitable carboxy-protecting groups include t-butyl and benzyl groups. Suitable tetrazole nitrogen-protecting groups include triphenylmethyl (Tr), benzyl, t-butyl, methoxymethyl, benzyloxymethyl, p-nitrobenzyl, 1-ethoxyethyl and the like.

The compounds of formula (I) may be prepared using the reactions and techniques described in this section. The reactions are performed in a solvent

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appropriate to the reagents and materials employed and suitable for the transformation being effected. It is understood by those skilled in the art of organic synthesis that the functionality present on the heterocycle and other portions of the molecule must be consistent with the chemical transformation proposed. This will frequently necessitate judgment as to the order of synthetic steps, protecting groups required and deprotection conditions. Throughout the following section, not all compounds of formula (I) falling into a given class may necessarily be prepared by all methods described for that class. Substituents on the starting materials may be incompatible with some of the reaction conditions required in some of the methods described. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternative methods described must then be used.

Schemes I - XV illustrate methods of preparing compounds of the invention comprising various -G-E- substituents.

Scheme I

Reaction Scheme I illustrates a method of preparing compounds wherein -G-E- is -N(R₅)-. According to Scheme I, a biphenylamine of Formula 82 is alkylated under standard conditions (e.g., R₅-X' wherein X' is a leaving group) and then reacted with a chloro-heterocycle to give a compound of Formula 81.

Scheme II

According to Scheme II, compounds wherein -G-E- is -O- are prepared by coupling a hydroxy-substituted heterocycle with a bromo-biphenyl compound of Formula 80 in the presence of a copper salt to give a compound of Formula 83.

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Scheme III

Reaction Scheme III illustrates a method of preparing compounds wherein -G-E- is -S-. According to Scheme XX, a biphenyl thiol of Formula 85 is reacted with a chloro-heterocycle to give a compound of Formula 84.

Scheme IV

Reaction Schemes IVA and IVB illustrate alternative methods of preparing compounds wherein -G-E- is $-\text{CH}_2\text{-N(R}_5\text{)-}$. According to Scheme IVA, a biphenylmethylaniline of the Formula 86 is reacted with a chloro-heterocycle in the presence of a base, such as triethylamine or lithium hexamethyldisilazide, to give a compound of Formula 87. Alternatively, according to Scheme IVB, a chloro-heterocycle is reacted with a primary amine to give a compound of Formula 88. This secondary amine is reacted with a biphenylmethyl bromide 89 to give a compound of Formula 87.

Scheme V

According to Scheme V, compounds wherein -G-E- is $-\text{CH(R}_5\text{)-NH-}$ are prepared by oxidizing a compound of Formula 90 to aldehyde 91. Addition of an organometallic reagent (e.g., $\text{R}_5\text{-M}$ is propyl-Grignard reagent, yields secondary alcohol 92. The alcohol is converted to a leaving group (e.g., X' is a mesylate) which is displaced with a heterocyclic amine to afford a compound of Formula 94.

Scheme VI

Reaction Schemes VIA and VIB illustrate alternative methods of preparing compounds wherein -G-E- is $-\text{CH(R}_5\text{)-O-}$. According to Scheme VIA, a compound of Formula 93 having a leaving group X' , e.g., mesylate, is reacted with a hydroxy-substituted heterocyclic in the presence of a base to give a compound of Formula 95. Alternatively, according to Scheme VIB, secondary alcohol 92, whose preparation is illustrated in Scheme XXII, is reacted with a chloro-heterocycle in the presence of a base to give a compound of Formula 95.

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Scheme VII

According to Scheme VII, compounds wherein -G-E- is -CH(R₅)-S- are prepared by reacting a compound of Formula 93, whose preparation is illustrated in Scheme XXII, with a thiol-substituted heterocycle in the presence of a base to give a compound of Formula 96.

Scheme VIII

According to Scheme VIII, compounds wherein -G-E- is -CH₂-CH(R₅)- are prepared by reacting a heterocyclic aldehyde of Formula 97 with a Wittig reagent (CH₂=P(Ph)₃) to yield vinyl-heterocycle 98. Olefin epoxidation with *m*-chloroperoxybenzoic acid affords epoxide 99. Epoxide 99 is opened with a Grignard reagent 100 prepared from the corresponding biphenylbromide. The resulting alcohol 101 is oxidized (e.g., Swern oxidation) to afford ketone 102. The ketone is reacted with the desired Wittig reagent (e.g., Pr-P(Ph)₃) to give an intermediate olefin which is reduced with hydrogen in the presence of a catalyst (e.g., platinum or palladium) to afford a compound of Formula 103.

Scheme IX

According to Scheme IX, compounds wherein -G-E- is -CH(R₅)-CH₂- are prepared by converting a biphenyl aldehyde of the Formula 91 to a halo-alkylated compound of the Formula 93A (X' is halogen). Compound 93A is converted into Wittig reagent 110 using triphenylphosphine and a suitable base. This Wittig reagent is reacted with heterocyclic aldehyde 97 to give a compound of the Formula 111. This olefin is reduced with hydrogen in the presence of a catalyst such as platinum or palladium to give a compound of the Formula 112.

Scheme X

According to Scheme X, compounds wherein -G-E- is -N(R₅)-CH₂- are prepared by alkylating amine 82 with R₅Cl in the presence of a base. The resulting amine 82a is reductively aminated with aldehyde 97 to give a compound of the Formula 114.

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Scheme XI

According to Scheme XI, compounds wherein -G-E- is -NH-CH(R₅)- are prepared by reacting a heterocyclic nitrile 115 with an alkyl Grignard reagent (e.g., propylmagnesium bromide) and then hydrolyzing the intermediate imine to give a ketone of the Formula 116. Reductive amination with a biphenylamine 82 yields a compound of the Formula 117.

Scheme XII

According to Scheme XII, compounds wherein -G-E- is -O-CH(R₅)- are prepared by reacting a heterocyclic aldehyde with an organometallic reagent (e.g., R₅-M is propylmagnesium bromide) to produce a secondary alcohol of the Formula 120. The alcohol is converted to a leaving group (for example, mesylate) and then is coupled with the biphenyl alcohol in the presence of a base to afford a compound of the Formula 121.

Scheme XIII

According to Scheme XIII, compounds wherein -G-E- is -S-CH(R₅)- are prepared by converting a secondary alcohol to a leaving group (e.g., X' is mesylate) and then displacing it with biphenyl thiol 85 in the presence of a base to afford a compound of the Formula 123.

Scheme XIV

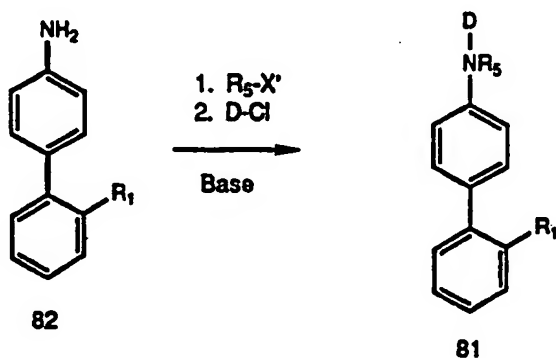
According to Scheme XIV, compounds wherein -G-E- is -NH-N(R₅)- are prepared by converting a biphenylamine 82 into a urea of the Formula 124. The urea is reacted with bromine in the presence of a base to yield hydrazine 125. Alkylation with an alkyl bromide (e.g., R₅X' is propyl bromide), followed by displacement of a chloro heterocycle with the secondary amine 125, affords a compound of the Formula 126.

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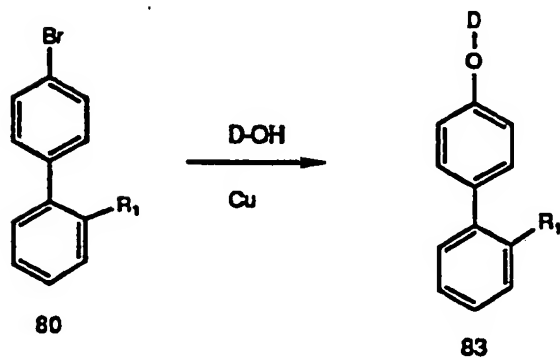
Scheme XV

According to Scheme XV, compounds wherein -G-E- is -N(R₅)-NH- are prepared by first converting amine 82a to urea 130. Urea 130 is converted to hydrazine 131 by treatment with bromine in base. Hydrazine 131 is reacted with chloro-heterocycle D-Cl to afford a compound of the Formula 132.

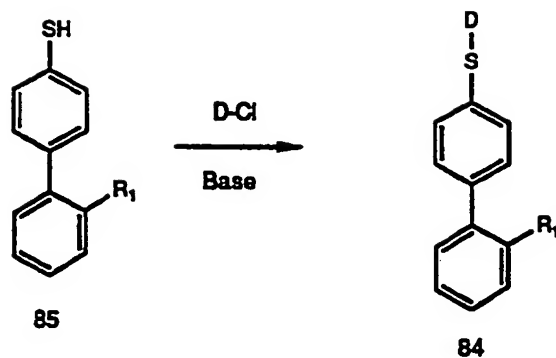
SCHEME I



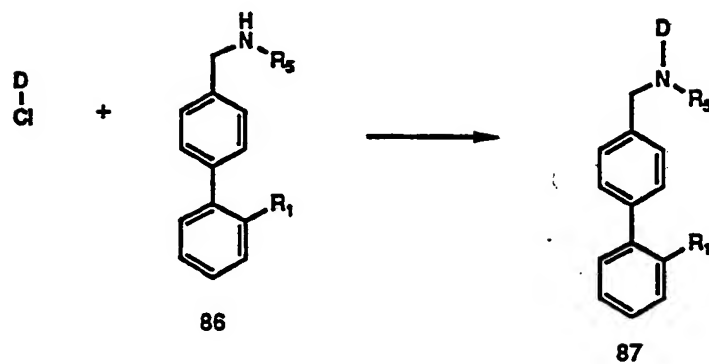
SCHEME II



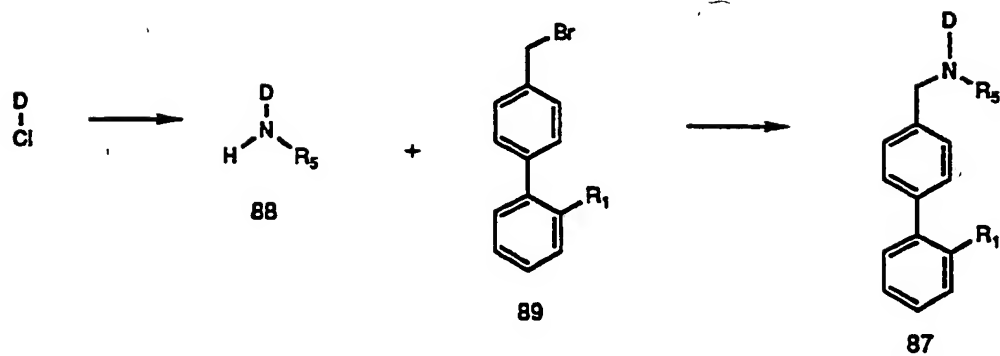
- 32 -
SCHEME III



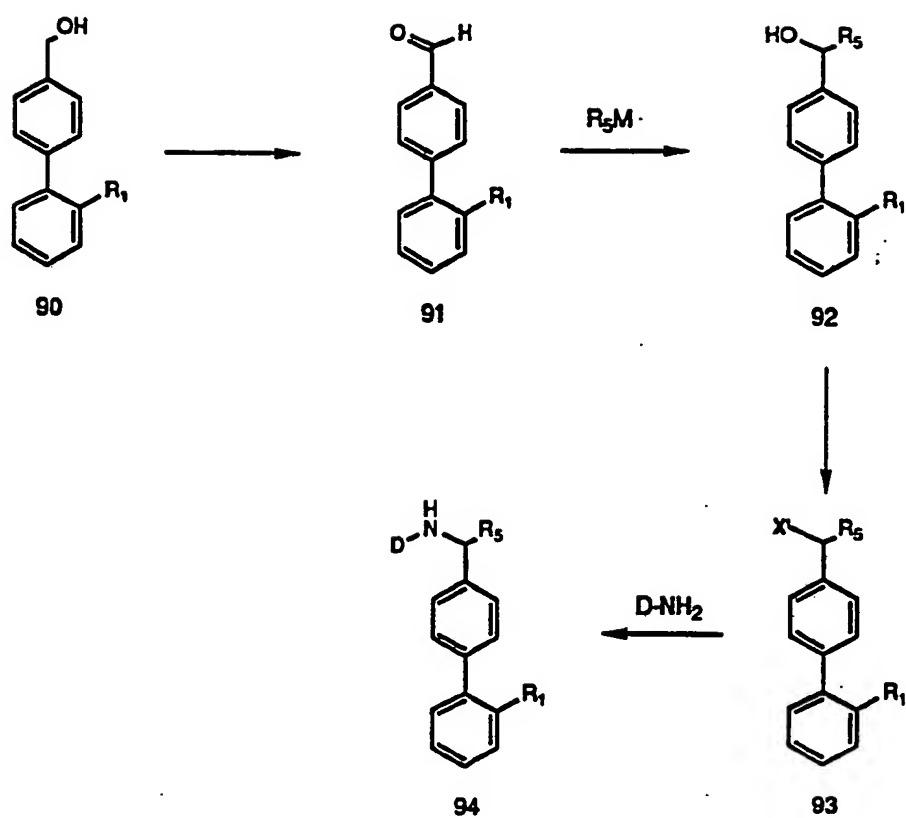
SCHEME IVA



SCHEME IVB

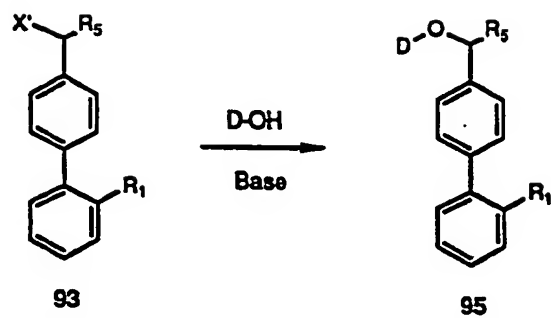


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SCHEME V

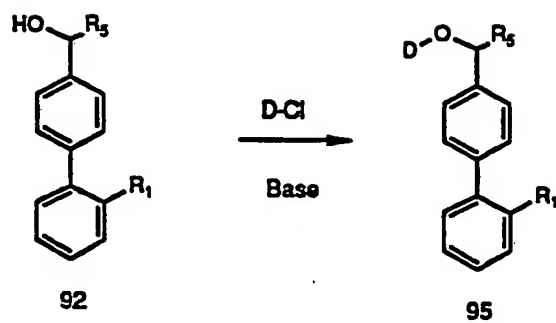


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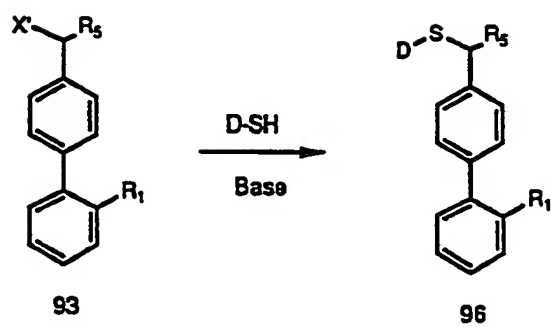
SCHEME VIA



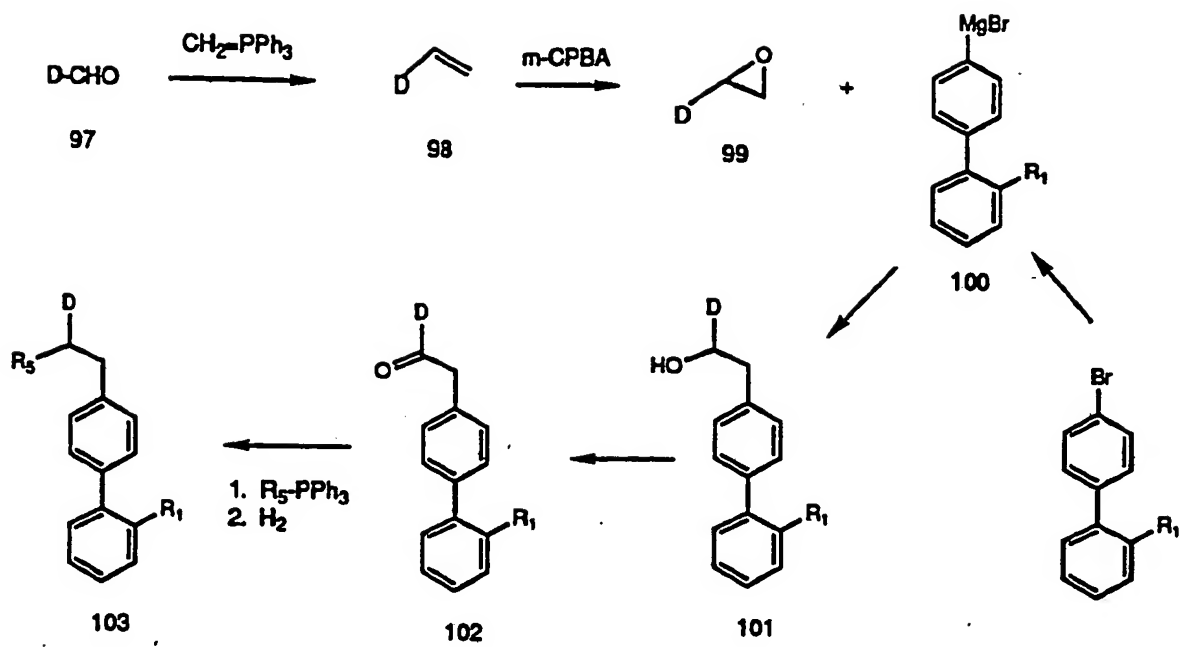
SCHEME VIB



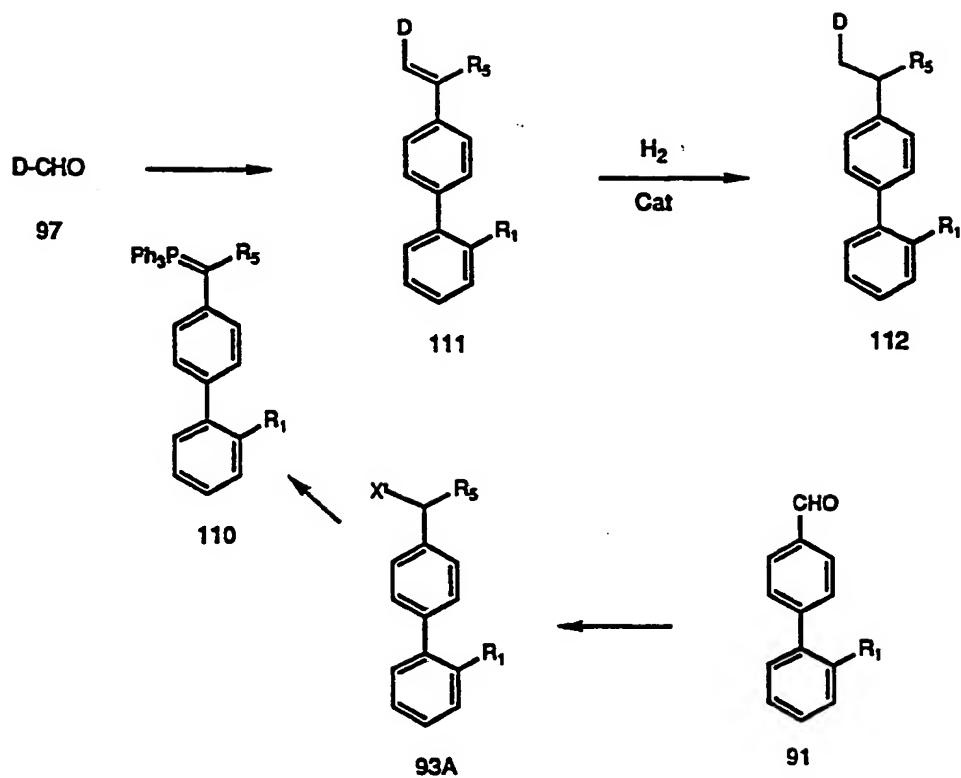
SCHEME VII



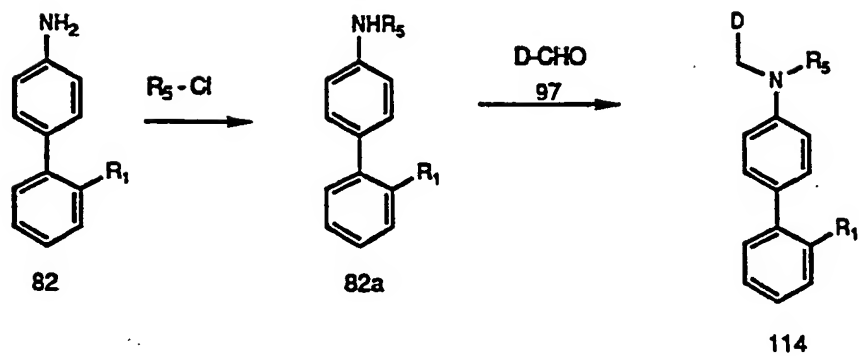
- 35 -
SCHEME VIII



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SCHEME IX

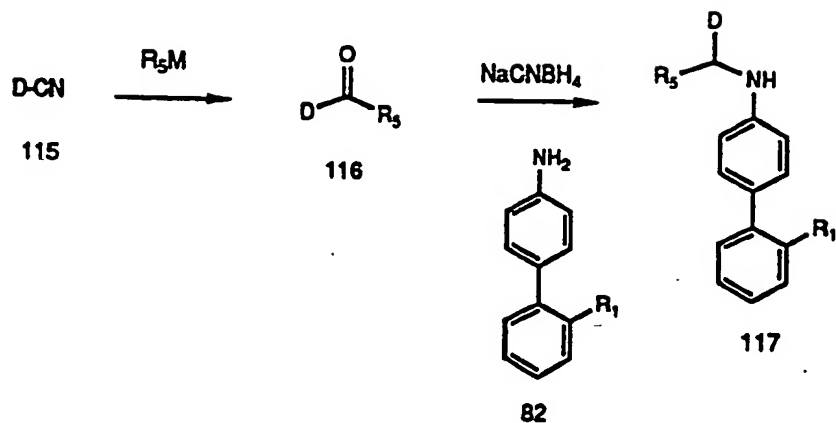


SCHEME X

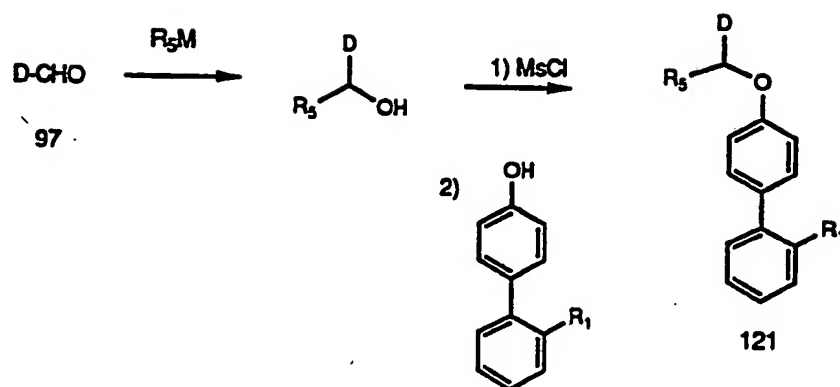


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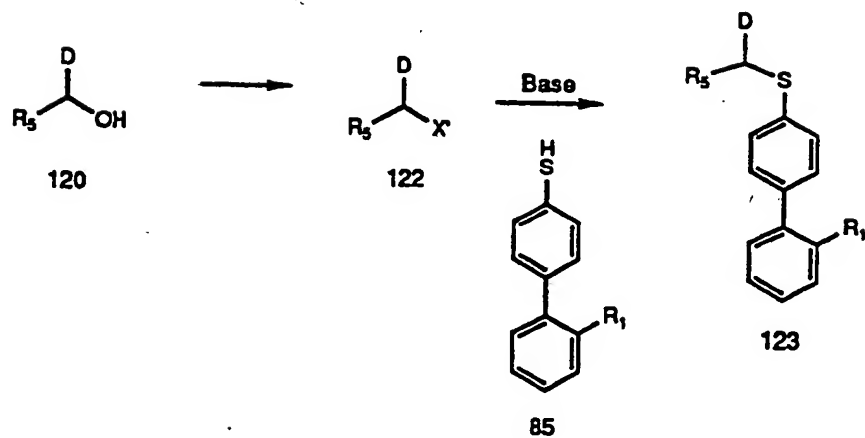
SCHEME XI



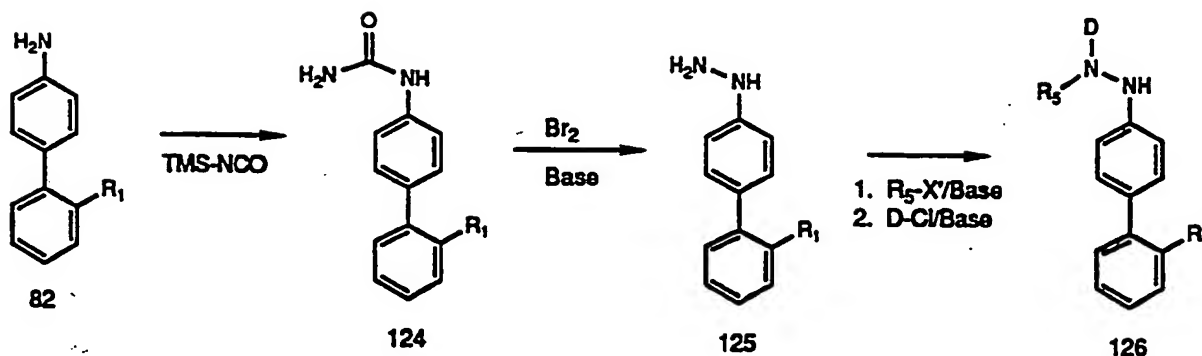
SCHEME XII



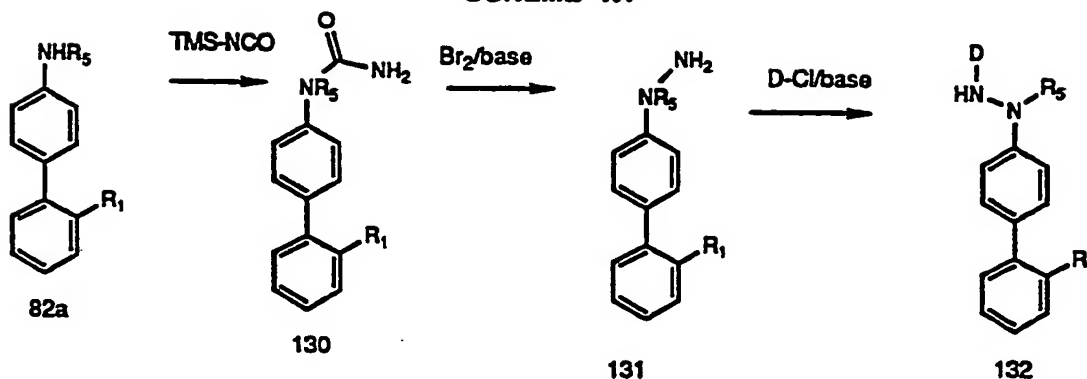
SCHEME XIII



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SCHEME XIV



SCHEME XV



Schemes XVI-XVII illustrate methods of preparing compounds of the invention comprising various bicyclic heterocyclic groups (D).

Scheme XVI

Scheme XVI discloses the synthesis of a compound of the invention comprising a substituted pyrrolopyridine (in particular, 4-[N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino]-1,3-dioxo-1,3-dihydropyrrolo[3,4-c]pyridine and 4-[N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino]-1,3-dioxo-2-hydroxy-1,3-dihydropyrrolo[3,4-c]pyridine). 3,5-Dichloro-1-methyl-2-(1H)-pyrazinone, prepared according to the method of Vekemans, Pollers-

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Wieers and Hoornaert, J. Het. Chem. 20, 919 (1983), is combined in ethanol with 1.0 equivalent of N-triphenylmethyl-5-[2-(4'-propylaminomethyl-biphenyl)]tetrazole, prepared by the procedure described in Example 72B, and 2.0 equivalents of ethyldiisopropylamine to afford a compound of the Formula 201. Compound 201 is dehalogenated using 10% palladium on carbon in 1:1 ethanol/ethyl acetate to give the des-chloro compound 202. Diels-Alder cycloaddition of compound 202 with dimethyl acetylenedicarboxylate (3 equivalents, neat) at 140 °C according to the method of Tutonda *et al.*, Tet. Letters 27, 2509 (1986) provides a compound of the Formula 203. Diester 203 is heated in a sealed tube with ethanolic ammonia at 100 °C overnight to give an imide of the Formula 204. Acid catalyzed detritylation affords a compound of the Formula 205.

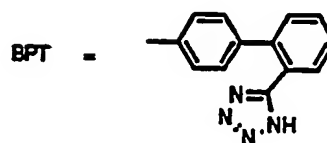
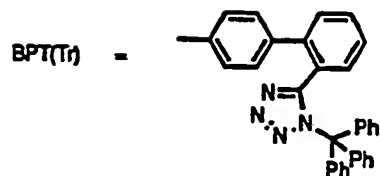
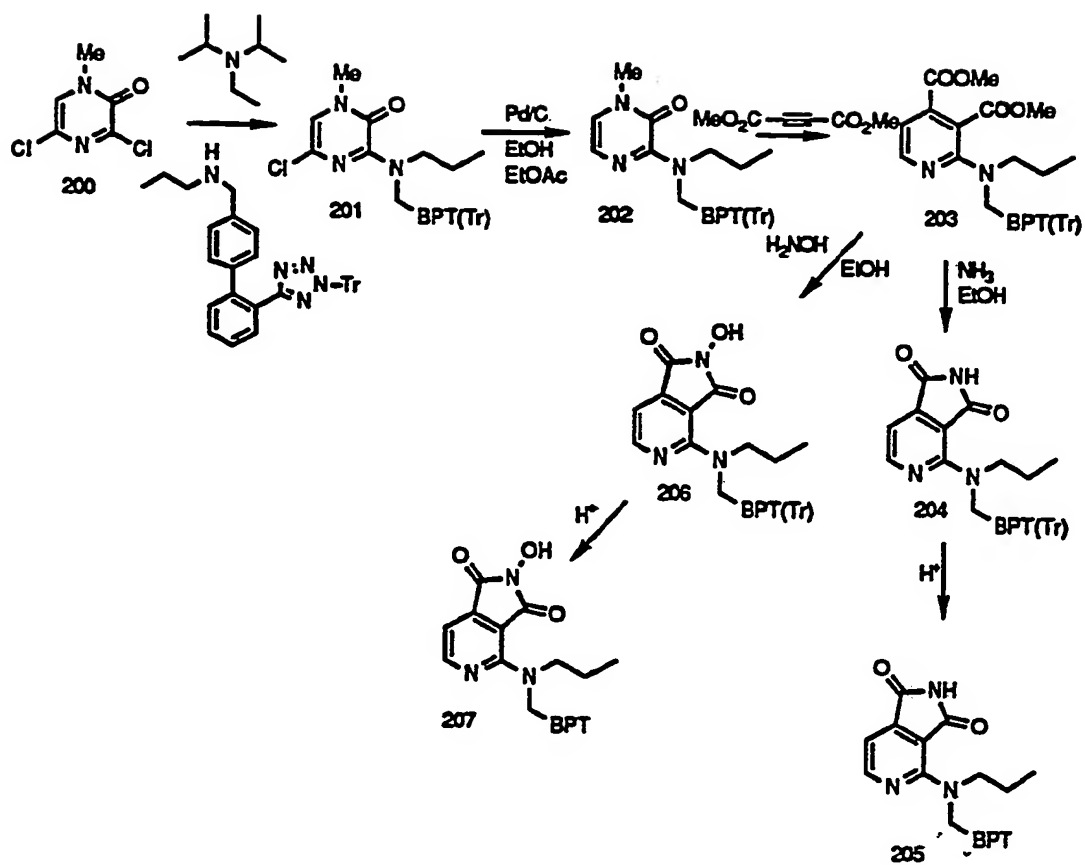
Alternatively, heating a compound of the Formula 203 in a sealed tube with hydroxylamine in ethanol at 80 °C overnight affords the corresponding N-hydroxyimide 206. Acid catalyzed detritylation affords a compound of the Formula 207.

Scheme XVII

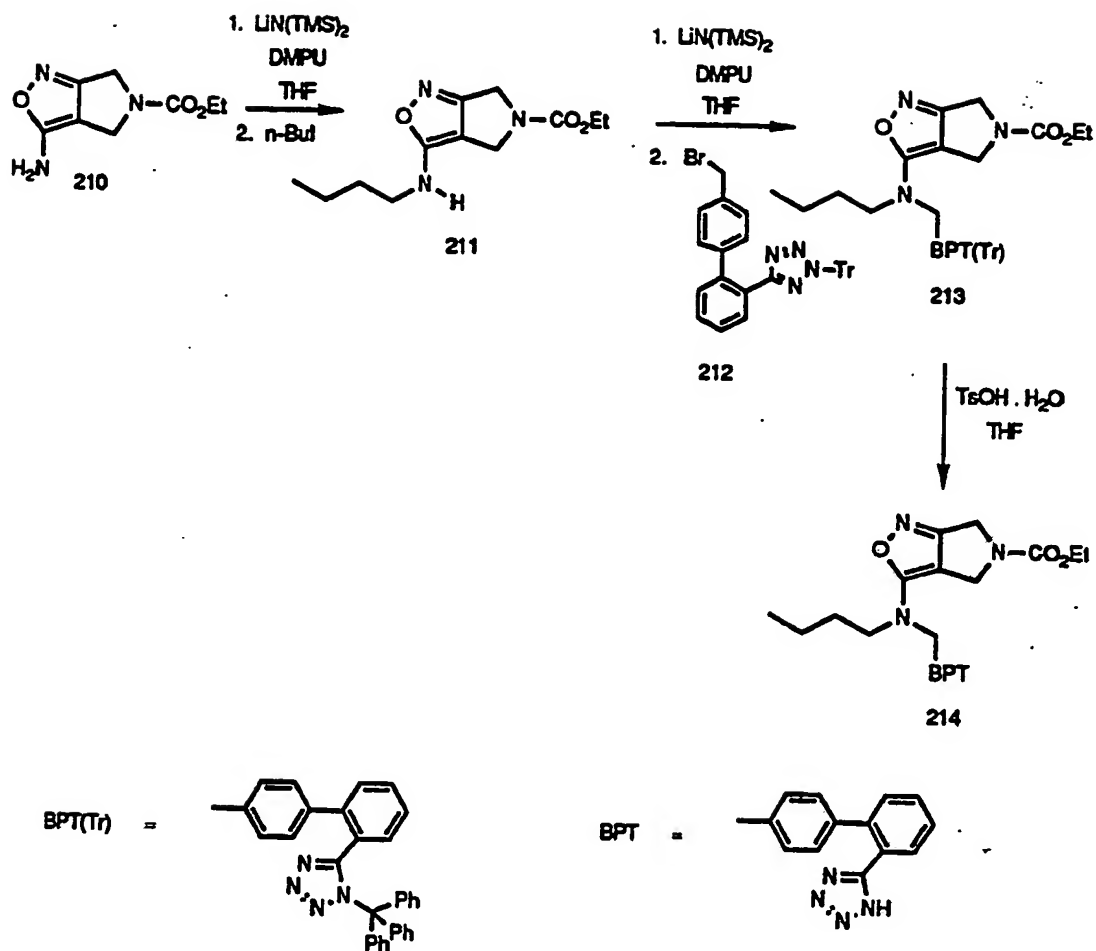
Scheme XVII discloses the synthesis of a compound of the invention comprising a substituted pyrroloisoxazole (in particular, ethyl 3-{N-butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-4H-pyrrolo[3,4-c]isoxazole-5(6H)-carboxylate). A compound of the Formula 210, ethyl 3-amino-4H-pyrrolo[3,4-c]isoxazole-5(6H)-carboxylate, prepared according to the procedure described in J. Med. Chem. 11, 453 (1968), is reacted with lithium bis(trimethylsilyl)amide and *n*-butyl iodide according to the procedures described in Example 6A to give the 3-butylamino compound of the Formula 211. Compound 211 is alkylated with N-triphenylmethyl-5-[2-(4'-bromomethyl-biphenyl)]tetrazole and lithium bis(trimethylsilyl)amide also by the procedure described in Example 6A to give a compound of the Formula 213. Tonic acid detritylation affords a compound of the Formula 214.

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SCHEME XVI

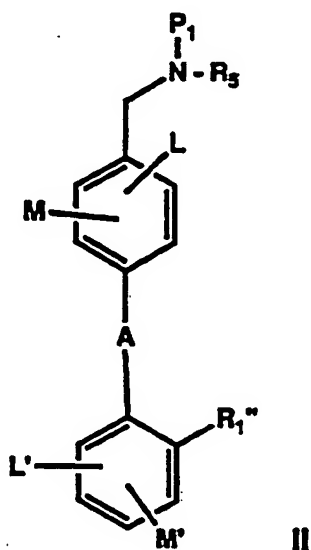


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SCHEME XVII



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Intermediates useful for the preparation of the novel compounds of this invention include a compound of the formula (II):



wherein A, L, L', M, M' and R₅ are defined as above;

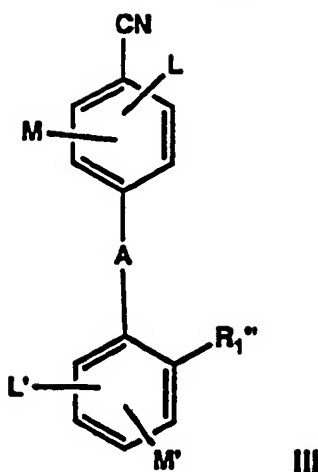
P₁ is hydrogen or an N-protecting group; and

R₁^{''} is R₁ as defined above, -NO₂, -CN or an N-protected tetrazolyl group wherein the tetrazole is N-protected with a trityl group, a t-butyl group, a benzyl group, a benzyloxymethyl group or a methoxymethyl group.

Preferred intermediates of formula II are those wherein A is a bond; L, L', M and M' are hydrogen; and R₁^{''} is a tetrazolyl group or an N-protected tetrazolyl group.

Other intermediates useful for the preparation of the novel compounds of this invention include a compound of the formula (III):

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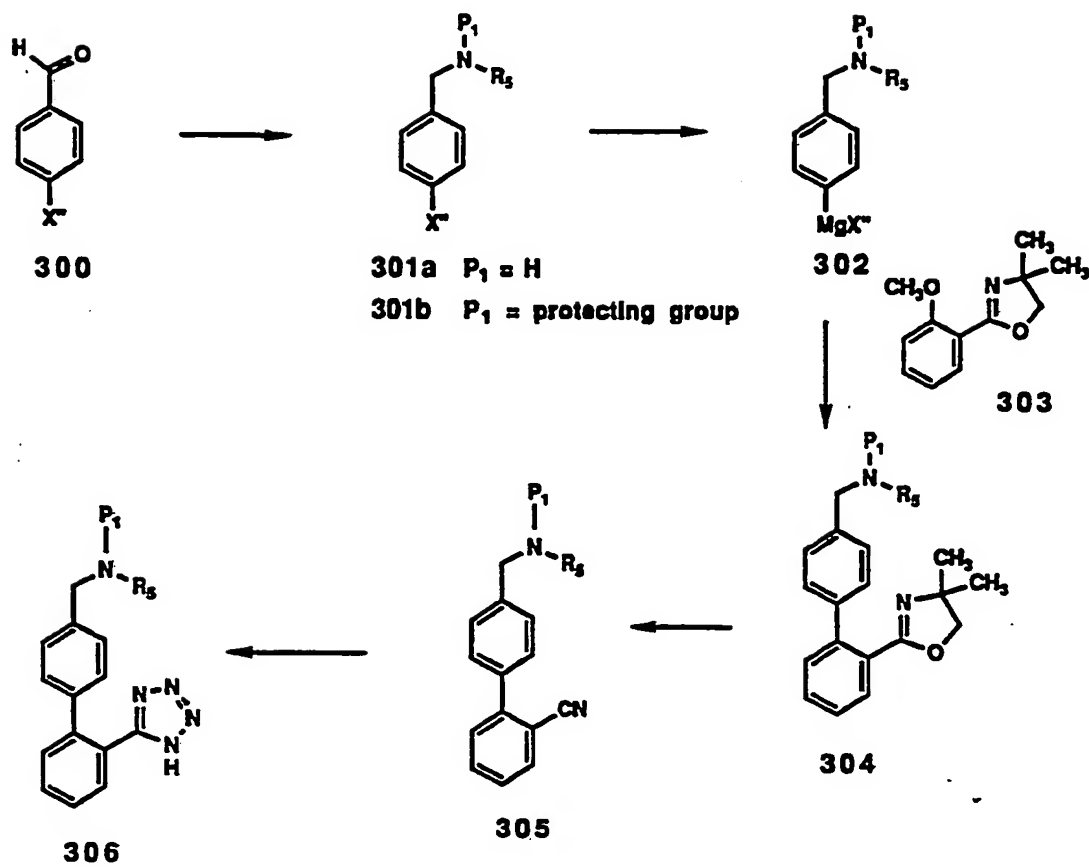
wherein A, L, L', M and M' are defined as above; and R₁^{''} is R₁ as defined above, -NO₂, -CN or an N-protected tetrazolyl group wherein the tetrazole is N-protected with a trityl group, a t-butyl group, a benzyl group, a benzyloxymethyl group or a methoxymethyl group.

Preferred intermediates of formula III are those wherein A is a bond; L, L', M and M' are hydrogen; and R₁^{''} is a tetrazolyl group or an N-protected tetrazolyl group.

Intermediates of the formula II wherein A is a covalent bond, L, L', M, and M' are hydrogen and R₁^{''} is a tetrazolyl group (i.e., compound 306) can be prepared as illustrated in Scheme XVIII. Aldehyde 300 (X^{''} is halogen) can be reductively aminated to provide amine 301a. Protection of the amino group (for example, P₁ = trityl), followed by Grignard formation, provides compound 302. Reaction of 302 with oxazoline 303 provides biphenyl 304. Reaction of biphenyl 304 with POCl₃ provides nitrile 305. Nitrile 305 can then be elaborated to tetrazole 306 (for example, by reaction with sodium azide).

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SCHEME XVIII



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The foregoing may be better understood from the following examples, which are presented for the purpose of illustration and not intended to limit the scope of the inventive concept.

Example 1

2-[N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino]-6,7-dihydro-5H-[1]-pyrindine-3-carboxylic acid

Example 1A

Ethyl 2-cyano-3-hydroxyacrylate sodium salt

Sodium (2.4 g, 105 mmol) was added portionwise to ethanol (40 mL). After complete dissolution, the solution was warmed to 50–60 °C and ethyl cyanoacetate (11.3 g, 0.10 mol) was added dropwise over two minutes. A white precipitate formed immediately upon addition. The mixture was stirred for an additional 10 minutes at 60 °C, and then ethyl formate (6.4 g, 0.10 mol) was added to the warm mixture. The mixture was heated to reflux, at which time the solids dissolved. After approximately three hours at reflux, a white precipitate formed. The resulting slurry was kept at reflux for three more hours and then allowed to cool to ambient temperature overnight. The white solid was collected by filtration, washed with cold ethanol and dried *in vacuo* at 50 °C to give the product as a white solid. (7.8 g, 48% yield). For analytical purposes, a small amount of the product (~25 mg) was neutralized with phosphoric acid, extracted with ethyl acetate, dried over sodium sulfate, and evaporated under reduced pressure to give a yellow oil which solidified on standing. ¹H NMR (CDCl₃, 300 MHz) δ 1.38 (t, J = 7Hz, 3H), 4.37 (q, J = 7Hz, 2H), 7.87 (bs, 1H), 12.8 (s, 1H).

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Example 1BEthyl 2-cyano-3-chloroacrylate

The compound resulting from Example 1A (2.5 g, 15 mmol) was taken up in phosphorous oxychloride (16 mL) and heated at reflux for three hours. The mixture was allowed to cool to ambient temperature and the volume reduced by one half under reduced pressure. The residue was diluted with diethyl ether (50 mL), and the solids which formed were collected by filtration and discarded. The filtrate was evaporated under reduced pressure to give a reddish oil which was distilled (80–81 °C at 0.75 mm Hg) to give the product as a colorless oil (1.16 g, 48% yield). ¹H NMR (CDCl₃, 300 MHz) δ 1.37 (t, J = 7Hz, 3H), 4.36 (q, J = 7Hz, 2H), 8.05 (s, 1H).

Example 1CEthyl 2-cyano-3-[(2-pyrrolidin-1-yl)-cyclopent-2-enyl]-acrylate

To 1-pyrrolidino-1-cyclopentene (0.99 g, 1.10 mL, 7.3 mmol) dissolved in methylene chloride (20 mL) was added triethylamine (0.74 g, 1.0 mL, 7.3 mmol). The solution was then cooled to -20 °C. The compound resulting from Example 1B (1.16 g, 7.3 mmol) was added dropwise over five minutes and then the solution was stirred at -20 °C for one hour. After warming to ambient temperature, the solution was washed with water (2 mL), dried over magnesium sulfate and evaporated under reduced pressure to give a red solid (2.0 g) which was used without further purification.

Example 1DEthyl 2-amino-6,7-dihydro-5H-[1]pyrindine-3-carboxylate

The compound resulting from Example 1C (2.0 g) was suspended in ethanolic ammonia (20 mL) and stirred at ambient temperature for four days. The solid was collected by filtration and washed with diethyl ether. The resulting bright yellow solid was added to a sodium ethoxide solution prepared from sodium (0.25 g) dissolved in ethanol (25 mL). The mixture

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was heated at reflux for 1.5 hours during which time the solution turned dark red. The solvent was removed under reduced pressure and the residue obtained was dissolved in ethyl acetate (50 mL), washed with water (2 x 50 mL), dried over sodium sulfate and evaporated under reduced pressure to give the product as an orange solid (0.83 g, 55% yield), which was used without further purification. ^1H NMR (CDCl_3 , 300 MHz) δ 1.38 (t, J = 8Hz, 3H), 2.84 (m, 4H), 4.32 (q, J = 9Hz, 2H), 6.34 (bs, 2 H), 7.96 (s, 1H). MS (DCI/NH_3) m/e 207 ($\text{M}+\text{H}$) $^+$.

Example 1E

Ethyl 2-(*n*-butylamino)-6,7-dihydro-5H-[1]pyrindine-3-carboxylate

To the compound resulting from Example 1D (0.28 g, 1.36 mmol) dissolved in tetrahydrofuran (1 mL) was added 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) (1 mL). The solution was cooled to 0 °C and lithium hexamethyldisilazide (1.4 mL of a 1N solution in THF) was slowly added. The ice-bath was removed and the solution stirred for 10 minutes. The reaction mixture was re-cooled in the ice-bath and butyl iodide (0.74 g, 0.46 mL, 4.02 mmol) was added. After the addition was complete, the bath was removed and the solution stirred at ambient temperature overnight. The reaction mixture was evaporated and dissolved in ethyl acetate (25 mL). The ethyl acetate solution was washed with water (25 mL) and brine (25 mL), dried and concentrated under reduced pressure to give a yellow solid. Purification by flash chromatography on silica gel eluting with 10% ethyl acetate in hexane afforded the desired product as a yellow oil (175 mg, 49% yield). ^1H NMR (CDCl_3 , 300 MHz) δ 0.96 (t, J = 7Hz, 3H), 1.36 (t, J = 7Hz, 3H), 1.44 (m, J = 8Hz, 2H), 1.57 (bs, 1H), 1.62 (m, J = 8Hz, 2H), 2.07 (p, J = 8Hz, 2H), 2.79 (t, J = 8Hz, 2H), 2.88 (t, J = 8Hz, 2H), 3.51 (t, J = 7Hz, 2H), 4.29 (q, J = 7Hz, 2H), 7.93 (s, 1H). MS (DCI/NH_3) m/e 263 ($\text{M}+\text{H}$) $^+$.

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Example 1EEthyl 2-[N-butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino]-6,7-dihydro-5H-[1,1]-pyrindine-3-carboxylate

The compound resulting from Example 1E (220 mg, 0.84 mmol) was dissolved in tetrahydrofuran (1.5 mL) and cooled to 0 °C in an ice bath. Lithium hexamethyldisilazide (0.85 mL of a 1N solution in THF) was added dropwise over one minute. The bath was removed and the solution stirred for 30 minutes. The bath was replaced and N-triphenylmethyl-5-[2-(4'-bromomethyl-biphenyl)]tetrazole (83% pure, 563 mg, 0.84 mmol), prepared by the procedure described in European Patent Application No. 291,969, in tetrahydrofuran (1 mL) was added dropwise over one minute. The bath was removed and the solution was stirred overnight at ambient temperature during which time the solution turned black. The solvent was evaporated under reduced pressure, and the residue obtained was dissolved in ethyl acetate, washed with water (5 mL), brine (5mL), and 1N phosphoric acid (5 mL), dried over sodium sulfate and evaporated under reduced pressure to give a yellow oil. Purification by flash chromatography on silica gel eluting with 10% ethyl acetate in hexane afforded the product as a yellow foam (188 mg, 30% yield). ¹H NMR (CDCl₃, 300 MHz) δ 0.70 (t, J = 7Hz, 3H), 1.16 (m, 2H), 1.33 (t, J = 7Hz, 3H), 1.45 (m, 2H), 2.10 (m, J = 8Hz, 2H), 2.84 (t, J = 8Hz, 4H), 3.22 (m, 2H), 4.30 (q, J = 7Hz, 2H), 4.58 (bs, 2H), 6.9 (d, J = 8Hz, 6H), 7.06 (q, J = 8Hz, 4H), 7.23 (m, 8H), 7.44 (m, 4H), 7.77 (bs, 1H), 7.88 (dd, J = 8Hz, 1Hz, 1H).

Example 1G2-[N-Butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino]-6,7-dihydro-5H-[1,1]-pyrindine-3-carboxylic acid

The compound resulting from Example 1F (183 mg, 0.25 mmol) was dissolved in THF (1 mL) and EtOH (1 mL). *p*-Toluene sulfonic acid (50 mg) was added and the reaction stirred overnight at ambient temperature. The solvent was removed under reduced pressure and the residue dissolved in MeOH (2 mL). Sodium hydroxide (2 mL of a 5 N solution) was added and

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the cloudy solution stirred at ambient temperature. After three hours thin layer chromatography indicated that starting material was still present. The reaction mixture was heated at 70 °C for 2.5 hours. The solution was cooled to ambient temperature and the solvents removed *in vacuo*. The residue was taken up in water (5 mL) and extracted with ethyl acetate (2 x 5 mL). The organic layer was acidified with 1N phosphoric acid, extracted with ethyl acetate (2 x 10 mL), dried over sodium sulfate and evaporated under reduced pressure to give a pale yellow solid. The solid was triturated with hexanes, filtered and dried overnight *in vacuo* at 60 °C to afford 103 mg (89% yield) of the title compound. ¹H NMR (CDCl₃, 300 MHz) δ 0.90 (t, J = 7Hz, 3H), 1.40 (m, 2H), 1.55 (bm, 2H), 2.26 (t, J = 8Hz, 2H), 3.10 (m, 4H), 3.66 (bm, 2H), 4.45 (bm, 2H), 6.92 (m, 4H), 7.20-7.60 (m, 4H), 7.93 (d, J = 8Hz, 2H), 8.32 (s, 1 H). MS (FAB) m/e 469 (M+H)⁺, 491 (M+Na)⁺. Anal calcd for C₂₇H₂₈N₆O₂: C, 69.21; H, 6.02; N, 17.94. Found: C, 69.08; H, 5.87; N, 17.00.

Example 2

9-Methyl-6-{N-butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-9H-purine

Example 2A

N-Butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amine

N-Triphenylmethyl-5-[2-(4'-bromomethyl-biphenyl)]tetrazole (6.00 g, 10.7 mmol), prepared by the procedure described in European Patent Application No. 291,969, was dissolved in 55 mL of tetrahydrofuran. *n*-Butylamine (40 mL) was added and the mixture kept at ambient temperature for 2 hours. The solution was concentrated at reduced pressure and the residue obtained taken up in chloroform. The solution was washed with dilute potassium hydroxide solution, dried over potassium carbonate and concentrated under reduced pressure to afford the title compound. ¹H NMR (CDCl₃, 300 MHz) δ 0.89 (t, J = 7Hz, 3H), 1.25-1.38

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(m, 2H), 1.42-1.52 (m, 2H), 2.60 (t, J = 7Hz, 3H), 3.68 (s, 2H), 6.85-6.95 (m, 4H), 7.08 (s, 2H), 7.20-7.51 (m, 16H), 7.92 (dd, J = 8Hz, 2Hz, 1H).

Example 2B

9-Methyl-6-(N-butyl-N-[(2'-[N-triphenylmethyl]-1H-tetrazol-5-yl)biphenyl-4-yl)methylamino]-9H-purine

A solution of the compound resulting from Example 2A (3 mmol) in tetrahydrofuran (25 mL) was treated with triethylamine (1 mL) and 9-methyl-6-chloropurine (800 mg, 4.75 mmol). The reaction mixture was stirred for 24 hours at 50 °C. An additional portion of 9-methyl-6-chloropurine (400 mg) was added and heating was continued for an additional 48 hours. The volatiles were removed *in vacuo* and the residue obtained dissolved in ethyl acetate (200 mL). The organic solution was washed with saturated aqueous brine, dried over sodium sulfate and sodium carbonate, filtered and concentrated *in vacuo*. The residue obtained was flash chromatographed on silica gel eluting with ethyl acetate in hexanes to afford the title compound as an amorphous solid (1.1 g, 65%). MS (FAB) m/e 682 (M+H)⁺.

Example 2C

9-Methyl-6-(N-butyl-N-[(2'-[1H-tetrazol-5-yl)biphenyl-4-yl)methylamino]-9H-purine

The compound resulting from Example 2B (500 mg, 0.75 mmol) was dissolved in tetrahydrofuran (25 mL) to which acetic acid (25 mL) and water (2 mL) had been added. The solution was refluxed for 2 hours and then concentrated under reduced pressure. The residue obtained was chromatographed on silica gel eluting with ethanol in methylene chloride to provide the title compound as a colorless amorphous solid (150 mg, 47%). ¹H NMR (DMSO-d₆, 300 MHz) δ 0.87 (t, J = 5Hz, 3H), 1.30 (m, 2H), 1.60 (m, 2H), 3.70 (bs, 2H), 3.72 (s, 3H), 4.10 (bs, 1H), 5.05 (bs, 1H), 5.50 (bs, 1H), 7.03 (d, J = 6Hz, 2H), 7.20 (d, J = 6Hz, 2H), 7.55 (m, 2H), 7.65 (m, 2H), 8.13 (s, 1H), 8.26 (s, 1H). MS (DCI/NH₃) m/e 440 (M+H)⁺.

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Example 3**6-(N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino)-9H-purine****Example 3A****6-(N-Butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino)-9H-purine**

To a solution of the compound resulting from Example 2A (4.8 mmol) in dimethylformamide (8 mL) was added triethylamine (1 mL) and 6-chloro-9-(tetrahydro-2-pyranyl)purine (1.5 g, 6.3 mmol). The reaction was heated for 6 hours at 65 °C and then stirred overnight at ambient temperature. The reaction mixture was worked up by the procedure described in Example 2B to give an oil. Flash chromatography on silica gel eluting with ethyl acetate in hexanes afforded the title compound as a yellow amorphous solid (2.4 g, 79%). MS (DCI/NH₃) m/e 752 (M+H)⁺.

Example 3B**6-(N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino)-9H-purine**

To the compound resulting from Example 3A (752 mg, 1 mmol) dissolved in tetrahydrofuran (50 mL) was added water (1.25 mL) and 12 N hydrochloric acid (1.25 mL). The solution was heated at 60 °C for 1 hour. The reaction was concentrated under reduced pressure and the residue obtained dissolved in methylene chloride (200 mL). The solution was extracted with saturated aqueous sodium bicarbonate. The combined aqueous extracts were washed with diethyl ether (100 mL) and then acidified with acetic acid and extracted with methylene chloride (3 x 100 mL). The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue obtained was crystallized from methylene chloride (25 mL) and hexane (250 mL). The solid was removed by filtration and dried to afford the title compound as a colorless amorphous solid (256 mg, 60%). ¹H NMR (DMSO-d₆, 300 MHz) δ 0.78 (t, J = 4.5 Hz, 3H), 1.20 (m, 2H), 1.50 (m, 2H), 3.80 (bs, 2H), 5.20 (bs,

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2H), 6.95 (d, J = 6Hz, 2H), 7.13 (d, J = 6Hz, 2H), 7.45-7.55 (m, 4H), 8.02 (s, 1H), 8.16 (s, 1H). MS (DCI/NH₃) m/e 426 (M+H)⁺.

Example 4

2-Chloro-6-[N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino]-9H-purine

Example 4A

N-Propyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amine

N-Triphenylmethyl-5-[2-(4'-bromomethyl-biphenyl)]tetrazole (6.00 g, 10.7 mmol), prepared by the procedure described in European Patent Application No. 291,969, was dissolved in 55 mL of tetrahydrofuran. *n*-Propylamine (40 mL) was added and the mixture kept at ambient temperature for 2 hours. The solution was concentrated at reduced pressure and the residue obtained taken up in chloroform. The solution was washed with dilute potassium hydroxide solution, dried over potassium carbonate and concentrated under reduced pressure to afford the title compound. ¹H NMR (CDCl₃, 300 MHz) δ 0.89 (t, J = 7Hz, 3H), 1.50 (sextet, J = 7Hz, 2H), 2.55 (t, J = 7Hz, 2H), 3.68 (s, 2H), 6.85-6.95 (m, 4H), 7.08 (s, 2H), 7.20-7.50 (m, 16H), 7.92 (dd, J = 8Hz, 2Hz, 1H).

Example 4B

2-Chloro-6-[N-propyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino]-9H-purine

To a solution of the compound resulting from Example 4A (2.3 mmol) in dimethylformamide (3 mL) was added triethylamine (1 mL) and 2,6-dichloropurine (600 mg, 3.2 mmol). The solution was heated for 12 hours at 50 °C and then additional 2,6-dichloropurine (600 mg) was added. Following an additional 2 hours at 50 °C, the reaction was worked up by the procedure described in Example 2B to afford an amorphous solid. Flash chromatography on silica gel eluting with ethyl acetate in hexane

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afforded the title compound as an off-white amorphous solid (1.15 g, 84%); MS (FAB) m/e 688 (M+H)⁺.

Example 4C

2-Chloro-6-[N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino]-9H-purine

The compound resulting from Example 4B (500 mg, 0.71 mmol) was deblocked using the procedure described in Example 2C. Flash chromatography on silica gel eluting with ethanol in methylene chloride containing acetic acid afforded the title compound as a colorless, amorphous solid (165 mg, 50%). ¹H NMR (DMSO-d₆, 300 MHz) δ 0.87 (t, J = 7.5Hz, 3H), 1.62 (m, 2H), 3.30 (bs, 1H), 3.48 (bs, 1H), 4.08 (bs, 1H), 4.90 (bs, 1H), 5.55 (bs, 1H), 7.05 (d, J = 8Hz, 2H), 7.20 (m, 2H), 7.50-7.70 (m, 4H), 8.15 (s, 1H). MS (DCI/NH₃) m/e 446 (M+H)⁺.

Example 5

6-[N-Propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino]-9H-purine

The compound resulting from Example 4A was reacted with 6-chloro-9-(tetrahydro-2-pyranyl)purine by the procedure described in Example 2B to provide an amorphous solid (950 mg, 56%). This compound was deprotected by the procedure described in Example 3B to afford the title compound as an amorphous solid (250 mg, 53%). ¹H NMR (DMSO-d₆, 300 MHz) δ 0.87 (t, J = 4.5Hz, 3H), 1.62 (m, 2H), 4.05 (bs, 2H), 5.05 (bs, 1H), 5.50 (bs, 1H), 7.02 (d, J = 6Hz, 2H), 7.20 (d, J = 6Hz, 2H), 7.50-7.70 (m, 4H), 8.10 (s, 1H), 8.20 (s, 1H). MS (FAB) m/e 412 (M+H)⁺.

Example 6

Ethyl 7-[N-butyl-N-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]amino]pyrazolo[1,5-a]pyrimidine-6-carboxylate

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Example 6AEthyl 7-(N-butylamino)pyrazolo[1,5-a]pyrimidine-6-carboxylate

To ethyl 7-aminopyrazolo[1,5-a]pyrimidine-6-carboxylate (3.70 g, 17.9 mmol, prepared by the procedure of Makisumi, Y., Chem. Pharm. Bull. **10**, 620 (1962), in dimethylformamide (90 mL) at 0 °C was added 1.0 M sodium bis(trimethylsilyl)amide in tetrahydrofuran (18 mL, 18 mmol). After 1 hour 1-iodobutane (2.2 mL, 19 mmol) was added, and the mixture was stirred at ambient temperature for 24 hours. The mixture was diluted with ethyl acetate and the solution washed with water and brine, dried over sodium sulfate and evaporated under reduced pressure. Chromatography of the residue obtained on silica gel eluting with 15% ethyl acetate in hexane afforded 1.73 g (37%) of the desired product as an oil. TLC (20% ethyl acetate/80% hexane) R_f = 0.27. ^1H NMR (CDCl_3 , 300 MHz) δ 0.98 (t, 3H), 1.40 (t, 3H), 1.56-1.42 (m, 2H), 1.80-1.65 (m, 2H), 4.43-4.30 (m, 4H), 6.42 (d, 1H), 7.98 (d, 1H), 8.68 (s, 1H), 9.67 (bs, 1H).

Example 6BEthyl 7-[N-butyl-N-[[2'-(N-triphenylmethyl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyrazolo[1,5-a]pyrimidine-6-carboxylate

To the compound resulting from Example 6A (1.73 g, 6.59 mmol) in dimethylformamide (30 mL) at 0 °C was added 1.0 M sodium bis(trimethylsilyl)amide in tetrahydrofuran (7.2 mL, 7.2 mmol). After 1 hour, triphenylmethyl-5-[2-(4'-bromomethylbiphenyl)]tetrazole (4.00 g, 6.03 mmol, 84% pure), prepared by the procedure of Aldrich, P. E. *et al.* European Patent Application 291,969, was added. The mixture was stirred at ambient temperature for 24 hours and at 50 °C for 18 hours. The mixture was diluted with ethyl acetate, and the solution was washed with water and brine, dried over sodium sulfate and evaporated under reduced pressure. Chromatography of the residue obtained on silica gel eluting with 14% ethyl acetate in hexane afforded 182 mg (4%) of the desired product as a foam. TLC (20% ethyl acetate/80% hexane) R_f = 0.17. ^1H NMR (CDCl_3 , 300 MHz) δ 0.78 (t, 3H), 1.25-1.10 (m, 2H), 1.38 (t, 3H), 1.60-1.46 (m, 2H), 3.67

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(t, 3H), 4.40 (q, 2H), 4.57 (s, 2H), 6.66 (d, 1H), 7.55-6.80 (m, 22H), 7.95-7.89 (m, 1H), 8.14 (d, 1H), 8.77 (s, 1H).

Example 6C

Ethyl 7-[N-butyl-N-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyrazolo[1,5-a]pyrimidine-6-carboxylate

The resultant compound from Example 6B (174.2 mg, 0.236 mmol) in 15:15:1 acetic acid/tetrahydrofuran/water (6 mL) was heated at reflux for 1 hour. The mixture was evaporated under reduced pressure and chased with several portions of toluene. Chromatography of the residue obtained on silica gel eluting with 2.5-4% methanol in chloroform afforded 94.7 mg (81%) of the title compound as a foam. TLC (10% methanol/90% chloroform) $R_f = 0.37$. ^1H NMR (CDCl_3 , 300 MHz) δ 0.86 (t, 3H), 1.35-1.10 (m, 2H), 1.37 (t, 3H), 1.72-1.55 (m, 2H), 3.40 (t, 2H), 4.38 (q, 2H), 4.98 (s, 2H), 6.64 (d, 1H), 7.22-7.10 (m, 4H), 7.46-7.38 (m, 1H), 7.63-7.51 (m, 2H), 8.17 (d, 1H), 8.29-8.22 (m, 1H), 8.54 (s, 1H).

Example 7

7-[N-Butyl-N-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid

The resultant compound from Example 6 (74.3 mg, 0.150 mmol) in 1 M aqueous potassium hydroxide solution (1.5 mL) was stirred for 46 hours at ambient temperature. The mixture was acidified with 6 M hydrochloric acid and filtered. The resulting solid was dissolved in tetrahydrofuran, dried over sodium sulfate and evaporated under reduced pressure. Chromatography of the residue on silica gel eluting with 5% methanol and 1% acetic acid in chloroform afforded 35.4 mg (50%) of the desired product as an amorphous solid. TLC (1% acetic acid/5% methanol/94% chloroform), $R_f = 0.22$. ^1H NMR (CDCl_3 , 300 MHz) δ 0.90 (t, 3H), 1.20-1.40 (m, 2H), 1.52-1.66 (m, 2H), 3.51-3.68 (m, 2H), 4.88 (s, 2H), 6.67 (s, 1H), 6.97 (d, 2H), 7.03 (d, 2H), 7.37 (dd, 1H), 7.47-7.62 (m, 2H), 8.17 (dd, 1H), 8.23 (d, 1H), 8.78 (s, 1H). MS (DCI/NH_3) m/e 469 ($\text{M}+\text{H}$) $^+$.

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Example 8

Ethyl 7-(N-butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino)-[1,2,3]triazolo[1,5-a]pyrimidine-6-carboxylate

Example 8A

Ethyl 7-(n-butylamino)-[1,2,3]triazolo[1,5-a]pyrimidine-6-carboxylate

Using the procedure described in Example 6A and replacing ethyl 7-aminopyrazolo[1,5-a]pyrimidine-6-carboxylate with ethyl 7-amino[1,2,3]-triazolo[1,5-a]pyrimidine-6-carboxylate, prepared using the method of Urleb, U. *et al.*, Heterocycles 24, 1899 (1986), affords the title compound.

Example 8B

Ethyl 5-(N-butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino)-[1,2,3]triazolo[1,5-a]pyrimidine-6-carboxylate

Using the procedure described in Example 6B with the resultant compound from Example 8A gives the title compound.

Example 8C

Ethyl 5-(N-butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino)-[1,2,3]triazolo[1,5-a]pyrimidine-6-carboxylate

Using the procedure described in Example 6C with the resultant compound from Example 8B gives the title compound.

Example 9

5-(N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino)-[1,2,3]triazolo[1,5-a]pyrimidine-6-carboxylic acid

The compound resulting from Example 8C is hydrolyzed by the procedure described in Example 7 to give the title compound.

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Example 10

6-(N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino)-8-methyl-9H-purine

Example 10A

6-(N-Butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino)-8-methyl-9H-purine

To a solution of the compound resulting from Example 2A (2.25 mmol) in dimethylformamide (3 mL) was added triethylamine (1 mL) and 6-chloro-8-methylpurine (0.39 g, 2.3 mmol), prepared by the procedure described in J. Chem. Soc. Perkin Trans. I, 879 (1984). The mixture was heated at 60 °C for 16 hours and then an additional portion of 6-chloro-8-methylpurine (160 mg, 0.954 mmol) was added. After 26 hours, the reaction was worked up by the procedure described in Example 2B. The residue obtained was purified using flash chromatography on silica gel eluting with ethanol in methylene chloride to provide the title compound as an amorphous solid (250 mg, 16%). MS (FAB) m/e 682 (M+H)⁺.

Example 10B

6-(N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino)-8-methyl-9H-purine

A solution of the compound resulting from Example 10A (240 mg, 0.35 mmol) in tetrahydrofuran (10 mL) was treated with *p*-toluene sulfonic acid monohydrate (100 mg, 0.53 mmol) and the mixture was stirred at ambient temperature for 12 hours. An additional aliquot of *p*-toluene sulfonic acid monohydrate (100 mg, 0.53 mmol) was added and the solution was heated at 60 °C for 4 hours. Potassium carbonate (280 mg, 2 mmol) was added and volatiles were removed under reduced pressure. Water (100 mL) was added to the residue and the solid was removed by filtration. The filtrate was acidified with acetic acid and the solid collected by filtration. Flash chromatography on silica gel eluting with ethanol and acetic acid in methylene chloride afforded the title compounds as an amorphous

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solid (90 mg, 58%) after recrystallization from ethyl acetate in hexane. ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ 0.87 (t, $J = 7.5\text{Hz}$, 3H), 1.30 (m, 2H), 1.55 (m, 2H), 2.42 (s, 3H), 3.80 (bs, 2H), 5.25 (bs, 2H), 7.03 (d, $J = 8\text{Hz}$, 2H), 7.16 (d, $J = 8\text{Hz}$, 2H), 7.50-7.70 (m, 4H), 8.13 (s, 1H), 12.70 (bs, 1H). MS (DCI/NH_3) m/e 440 ($\text{M}+\text{H}$) $^+$.

Example 11

7-(N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino)-1-methyl-1H-[1.2.3]triazolo[4.5-d]pyrimidine

Example 11A

4-Chloro-1-methyl-1H-[1.2.3]triazolo[4.5-d]pyrimidine

A suspension of 5-amino-6-chloro-4-methylaminopyrimidine (1.6 g, 10 mmol) in 30 mL of water was treated with 25 mL of acetic acid. The solution was diluted with 50 mL of water and solid sodium nitrile (760 mg, 11 mmol) was added. After stirring at ambient temperature for 15 minutes, an additional portion of sodium nitrite (140 mg, 2 mmol) was added. Stirring was continued for 15 minutes after which time the reaction mixture was diluted with 250 mL of water. Solid sodium acetate was added to adjust the pH to 5 and then the solution was extracted with ethyl acetate (2 x 250 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford the title compound as a pale yellow solid (1.2 g, 70%). ^1H NMR (CDCl_3 , 300 MHz) δ 4.38 (s, 3H), 8.95 (s, 1H).

Example 11B

7-(N-Butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino)-1-methyl-1H-[1.2.3]triazolo[4.5-d]pyrimidine

A solution of the compound resulting from Example 11A (430 mg, 2.5 mmol) in tetrahydrofuran (15 mL) was treated with triethylamine (1 mL) and the compound resulting from Example 2A (2.5 mmol). After stirring at

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ambient temperature for 10 hours, the volatiles were removed under reduced pressure and the residue obtained worked up by the procedure described in Example 2B. The residue obtained was purified by flash chromatography on silica gel eluting with ethyl acetate in hexane to afford the title compound as an amorphous solid (1.05 g, 61%). MS (FAB) m/e 683 (M+H)⁺.

Example 11C

7-(N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino)-1-methyl-1H-[1,2,3]triazolo[4,5-d]pyrimidine

To the compound resulting from Example 11B (300 mg, 0.44 mmol) dissolved in 10 mL of tetrahydrofuran was added *p*-toluene sulfonic acid monhydrate (92 mg, 0.48 mmol). The reaction was stirred at 55 °C for 3 hours. Solid potassium carbonate (200 mg) and 1 mL of water were added. The volatiles were removed under reduced pressure and water (75 mL) was added to the residue. The solid was removed by filtration and the filtrate was acidified with acetic acid. The aqueous layer was extracted with ethyl acetate (150 mL). The organic layer was washed with saturated aqueous sodium chloride and dried over sodium sulfate. The filtered solution was concentrated under reduced pressure and the residual acetic acid removed by azeotropic distillation with toluene. The residue was recrystallized from ethyl acetate and hexane to afford the title compound as an amorphous solid (120 mg, 61%). The 300 MHz ¹H NMR spectrum was found to be consistent with the proposed structure. MS (FAB) m/e 441 (M+H)⁺. Anal calcd for C₂₃H₂₄N₁₀: C, 62.71; H, 5.49; N, 31.80. Found: C, 62.82; H, 5.54; N, 31.68.

Example 12

6-(N-Propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino)-7-methyl-7H-purine

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Example 12A2,8-Dichloro-6-[N-propyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino]-7-methyl-7H-purine

To a solution of the compound resulting from Example 4A (4.33 mmol) in dimethylformamide (5 mL) was added triethylamine (1 mL) and 2,8-dichloro-7-methylpurine (1.00 g, 4.3 mmol). After stirring for 24 hours at ambient temperature, the reaction was worked up according to the procedure described in Example 2B. Flash chromatography on silica gel eluting with ethyl acetate in hexane afforded the title compound as a yellow amorphous solid (2.00 g, 75%). MS (FAB) m/e 736 (M+H)⁺.

Example 12B6-[N-Propyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino]-7-methyl-7H-purine

The compound resulting from Example 12A (1.00 g, 1.4 mmol) was mixed with 12 mL of triethylamine and 500 mg of 10% palladium on carbon in 150 mL of ethyl acetate. The mixture was stirred for 36 hours under 1 atmosphere of hydrogen. Additional aliquots of 10% palladium on carbon (500 mg) were added at 12 and 24 hours. The reaction mixture was filtered and concentrated under reduced pressure. The residue obtained was suspended in ethyl acetate (200 mL), washed with saturated brine and dried over sodium sulfate. The filtered solution was concentrated *in vacuo*. Flash chromatography on silica gel eluting with isopropanol and acetic acid in methylene chloride afforded the title compound as an amorphous solid (340 mg, 36%). MS (FAB) m/e 668 (M+H)⁺.

Example 12C6-[N-Propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino]-7-methyl-7H-purine

The compound resulting from Example 12B (330 mg, 0.5 mmol) was deprotected according to the procedure described in Example 2C. The residue obtained was purified by flash chromatography on silica gel eluting

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with formic acid and water in ethyl acetate. The residue obtained was recrystallized from methylene chloride and hexane to afford the title compound as an amorphous solid (150 mg, 68%). ^1H NMR (DMSO- d_6 , 300 MHz) δ 0.87 (t, $J = 7.5\text{Hz}$, 3H), 1.68 (m, 2H), 3.40 (m, 2H), 3.80 (s, 3H), 4.80 (s, 2H), 7.07 (d, $J = 9\text{Hz}$, 2H), 7.28 (d, $J = 9\text{Hz}$, 2H), 7.52-7.70 (m, 4H), 8.57 (s, 1H), 8.63 (s, 1H). MS (DCI/ NH_3) m/e 426 ($\text{M}+\text{H}$) $^+$.

Example 13

6-(N-Propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino)-9-(carboxymethyl)-9H-purine

Example 13A

6-Chloro-9-(*tert*-butyloxycarbonylmethyl)-9H-purine and 6-Chloro-7-(*tert*-butyloxycarbonylmethyl)-7H-purine

To a solution of 6-chloropurine (2.00 g, 12.9 mmol) in anhydrous dimethylformamide (10 mL) was added potassium carbonate (3.00 g) followed by *tert*-butylchloroacetate (2.00 g, 13.3 mmol). After stirring at ambient temperature for 14 hours, the reaction mixture was poured into saturated aqueous ammonium chloride solution (150 mL) and extracted with ethyl acetate (5 x 100 mL). The combined organic extracts were washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure to afford an orange oil. The reaction was repeated using 3.00 g of 6-chloropurine and the products were combined. Purification by flash chromatography on silica gel eluting with ethyl acetate in hexane provided the title compound (6.4 g, 75%). TLC (75% ethyl acetate/25% hexane) $R_f = 0.69$. MS (DCI/ NH_3) m/e 269 ($\text{M}+\text{H}$) $^+$, 286 ($\text{M}+\text{H}+\text{NH}_3$) $^+$.

Also obtained was the isomeric 7-substituted compound, 6-chloro-7-(*tert*-butyloxycarbonylmethyl)-7H-purine, (1.3 g, 15%). TLC (75% ethyl acetate/25% hexane) $R_f = 0.28$. MS (DCI/ NH_3) m/e 269 ($\text{M}+\text{H}$) $^+$, 286 ($\text{M}+\text{H}+\text{NH}_3$) $^+$.

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Example 13B**6-[N-Propyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino]-9-(tert-butyloxycarbonylmethyl)-9H-purine**

A solution of the compound resulting from Example 4A (3 mmol) in dimethylformamide (5 mL) was treated with triethylamine (1 mL) and the compound resulting from Example 13A (900 mg, 3.3 mmol). After stirring at 55 °C for 18 hours, the reaction was worked up by the procedure described in Example 2B. Flash chromatography on silica gel eluting with ethyl acetate in methylene chloride provided the title compound as a yellow amorphous solid (1.52 g, 76%). MS (FAB) m/e 768 (M+H)⁺.

Example 13C**6-[N-Propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino]-9-(carboxymethyl)-9H-purine**

A solution of the resultant compound from Example 13B (770 mg, 1 mmol) in tetrahydrofuran (75 mL) was treated with 12 N hydrochloric acid (3 mL) and water (2 mL). The solution was heated at 65 °C for 1.5 hours and then concentrated under reduced pressure. Water (100 mL) was added to the residue and solid sodium hydroxide was added to adjust the pH to 11. The solid was removed by filtration and the filtrate acidified with formic acid. The solid was collected by filtration and purified by flash chromatography on silica gel eluting with water and formic acid in ethyl acetate. The residue obtained was treated with toluene in methanol and concentrated *in vacuo* to afford the title compound as an amorphous solid (225 mg, 48%). ¹H NMR (DMSO-d₆, 300 MHz) δ 0.87 (t, J = 7Hz, 3H), 1.65 (m, 2H), 3.30 (bs, 2H), 5.01 (s, 2H), 5.02 (bs, 1H), 5.40 (bs, 1H), 7.02 (d, J = 8Hz, 1H), 7.21 (d, J = 8Hz, 2H), 7.50-7.70 (m, 2H), 8.16 (s, 1H), 8.23 (s, 1H). MS (DCI/NH₃) m/e 470 (M+H)⁺.

Example 14**6-[N-Propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino]-7-(carboxymethyl)-7H-purine**

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Example 14A6-{N-Propyl-N-[(2'-[N-triphenylmethyl]-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-7-(carboxymethyl)-7H-purine

A solution of the compound resulting from Example 4A (3 mmol) in dimethylformamide (5 mL) was treated with triethylamine (1 mL) and the 7-substituted isomer resulting from Example 13A (900 mg, 3.34 mmol). After stirring at 55 °C for 18 hours, an additional aliquot of the 7-substituted isomer (200 mg, 0.74 mmol) was added. Heating at 55 °C was continued for 24 hours at which time the reaction mixture was worked up by the procedure described in Example 2B. The residue obtained was purified by flash chromatography on silica gel eluting with ethyl acetate to afford the title compound as an amorphous solid (850 mg, 42%). MS (FAB) m/e 768 (M+H)⁺.

Example 14B6-{N-Propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-7-(carboxymethyl)-7H-purine

The compound resulting from Example 14A (770 mg, 1 mmol) was deprotected by the procedure described in Example 13C except that the solution was refluxed for 2 hours. Work up as described in Example 13 and flash chromatography on silica gel eluting with formic acid and water in ethyl acetate provided the title compound as an off-white amorphous solid (275 mg, 60%). ¹H NMR (DMSO-d₆, 300 MHz) δ 0.71 (t, J = 7.5Hz, 3H), 1.52 (m, 2H), 3.20 (m, 2H), 4.58 (s, 2H), 5.13 (s, 2H), 7.01 (d, J = 8Hz, 2H), 7.13 (d, J = 8Hz, 2H), 7.48-7.66 (m, 4H), 8.47 (s, 1H), 8.51 (s, 1H). MS (DCI/NH₃) m/e (M+H)⁺.

Example 159-Benzyl-6-{N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-9H-purine

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Example 15A9-Benzyl-6-chloropurine

The reaction of 6-chloropurine (5.00 g, 32.3 mmol), benzyl bromide (6.1 g, 35.6 mmol) and potassium carbonate (13.8 g, 100 mmol) in dimethylformamide (10 mL) according to the procedure described in Example 13A provided the title compound as a colorless solid (4.5 g, 57%).

Example 15B9-Benzyl-6-{N-propyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-9H-purine

To a solution of the compound resulting from Example 4A (2.53 mmol) in dimethylformamide (8 mL) was added triethylamine (3 mL) followed by the compound resulting from Example 15A (680 mg, 2.5 mmol). After stirring at 60 °C for 6 hours, the reaction was worked up according to the procedure described in Example 2B. Purification by flash chromatography afforded the title compound as a yellow amorphous solid (980 mg, 52%).

Example 15C9-Benzyl-6-{N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-9H-purine

The compound resulting from Example 15B (950 mg, 1.3 mmol) was deblocked according to the procedure described in Example 2C. Purification by flash chromatography eluting with ethanol and acetic acid in methylene chloride followed by recrystallization of the residue from methylene chloride and hexane afforded the title compound as an off white amorphous solid (570 mg, 89%). ¹H NMR (DMSO-d₆, 300 MHz) δ 0.87 (t, J = 7Hz, 3H), 1.63 (m, 2H), 3.45 (bs, 1H), 4.05 (bs, 1H), 5.00 (bs, 1H), 5.40 (s, 2H), 5.50 (bs, 1H), 7.05 (d, J = 8Hz, 2H), 7.20 (d, J = 8Hz, 2H), 7.25-7.45 (m, 5H), 7.50-7.70 (m, 4H), 8.26 (s, 1H), 8.32 (s, 1H).

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Example 162-Methyl-7-{N-butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}thiazolo[5,4-d]pyrimidine

Reaction of the compound resulting from Example 2A and 2-methyl-7-chlorothiazolo[5,4-d]pyrimidine, prepared according to the procedure described in Chem. Pharm. Bull. 16, 352 (1958), according to the procedure described in Example 15B affords 2-methyl-7-{N-propyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}thiazolo[5,4-d]pyrimidine.

The above compound is deblocked according to the procedure described in Example 2C to afford the title compound.

Example 172-Methyl-7-{N-butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}oxazolo[5,4-d]pyrimidine

Reaction of the compound resulting from Example 2A and 7-chloro-2-methyloxazolo[5,4-d]pyrimidine, prepared according to the procedure described in Chem. Pharm. Bull. 8, 137 (1960), according to the procedure described in Example 15B affords 2-methyl-7-{N-propyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}oxazolo[5,4-d]pyrimidine.

The above compound is deblocked according to the procedure described in Example 1G to afford the title compound.

Example 184-{N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-1H-pyrazolo[3,4-d]pyrimidine

The reaction of the compound resulting from Example 2A and 4-methylmercapto-6-chloropyrazolo[3,4-d]pyrimidine, prepared according to J. Am. Chem. Soc. 79, 6407 (1957), according to the procedure described in Example 15B affords 4-{N-propyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-1H-pyrazolo[3,4-d]pyrimidine.

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The above compound is deblocked according to the procedure described in Example 2C to afford the title compound.

Example 19

4-{N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-7-methyl-7H-pyrrolo[2,3-d]pyrimidine

Reaction of the compound resulting from Example 2A and 4-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidine, prepared according to the procedure described in Chim. Ther. 6(6), 427 (1971), according to the procedure described in Example 15A affords 4-{N-butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-7-methyl-7H-pyrrolo[2,3-d]pyrimidine.

The above compound is deblocked according to the procedure described in Example 2C to afford the title compound.

Example 20

4-{N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}thieno[2,3-d]pyrimidine

The compound resulting from Example 2A and 4-chlorothieno[2,3-d]pyrimidine, prepared according to the procedure described in Bull. Chim. Soc. Fr. 587 (1975), are reacted according to the procedure described in Example 15A to give 4-{N-butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}thieno[2,3-d]pyrimidine.

The above compound is deblocked according to the procedure described in Example 2C to afford the title compound.

Example 21

4-{N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-6-methyl-furo[2,3-d]pyrimidine

The compound resulting from Example 2A and 4-chloro-6-methyl-furo[2,3-d]pyrimidine, prepared according to the procedure described in Bull. Chem. Soc. Fr. 4344 (1969), are reacted according to the procedure

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described in Example 15A to afford 4-{N-butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-6-methyl-furo[2,3-d]pyrimidine.

The above compound is deblocked according to the procedure described in Example 1G to afford the title compound.

Example 22

7-[N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino]benzofuran

A mixture of 7-aminobenzofuran hydrochloride, prepared according to the procedure described in J. Med. Chem. **16**, 717 (1973), *n*-butyl iodide, and potassium carbonate are heated until the starting benzofuran is consumed. The reaction mixture is diluted with methylene chloride and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by flash chromatography to afford 7-butylaminobenzofuran.

A solution of the above compound in dimethylformamide is treated with potassium carbonate and N-triphenylmethyl-5-[2-(4'-bromomethyl-biphenyl)]tetrazole, prepared as described by P.E. Aldrich, *et al.*, in European Patent Application Number 291969. Stirring is continued at ambient temperature until the reaction is judged complete by TLC. The reaction is worked up following the procedure described above to afford 6-{N-butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}benzofuran.

The above compound is deblocked according to the procedure described in Example 1G and purified by flash chromatography on silica gel to afford the title compound.

Example 23

4-[N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino]-3-methyl-isoxazolo[5,4-b]pyridine

A solution of the compound resulting from Example 2A, triethylamine, and 4,6-dichloro-3-methylisoxazolo[5,4-b]pyridine, prepared according to the procedure described in J. Hetero. Chem. **14**, 435 (1977), in tetrahydrofuran are stirred at ambient temperature until the starting amine is

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consumed. The reaction is worked up according to the procedure described in Example 2B and purified by flash chromatography on silica gel to afford 4-{N-butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-6-chloro-3-methyl-isoxazolo[5,4-b]pyridine.

A solution of the above compound in dioxane is treated with hydrazine hydrate. Stirring is continued until the starting material is consumed. The reaction mixture is concentrated under reduced pressure and toluene is added. This solution is treated with 2 N sodium hydroxide solution and air is bubbled into the reaction mixture until the starting material is consumed. The organic layer is separated, washed with water, dried over calcium chloride and concentrated *in vacuo* to afford 4-{N-butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-3-methyl-isoxazolo[5,4-b]pyridine.

The above compound is deblocked according to the procedure described in Example 2C to afford the title compound.

Example 24

7-{N-Butyl-N-[(2'-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-1,3-dioxo-2-phenyl-1,3-dihydropyrrolo[3,4-c]pyridine-6-carboxylic acid

The reaction of *n*-butyl iodide, potassium carbonate and 7-amino-6-ethoxycarbonyl-1,3-dioxo-2-phenyl-1,3-dihydropyrrolo[3,4-c]pyridine, prepared according to the procedure described in Chem. Pharm. Bull. 31, 3460 (1983), according to the procedure described in Example 22 affords ethyl 7-butylamino-1,3-dioxo-2-phenyl-1,3-dihydropyrrolo[3,4-c]pyridine-6-carboxylate.

The above compound is treated with potassium carbonate and N-triphenylmethyl-5-[2-(4'-bromomethyl-biphenyl)]tetrazole, prepared as described by P.E. Aldrich, *et al.*, in European Patent Application Number 291969, by the procedure described in Example 22. Work up and flash chromatography on silica gel affords ethyl 7-{N-butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-1,3-dioxo-2-phenyl-1,3-dihydropyrrolo[3,4-c]pyridine-6-carboxylate.

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The above compound is deblocked and hydrolyzed by the procedure described in Example 1G to afford the title compound.

Example 25

9-Methyl-8-phenyl-6-(N-butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino)-9H-purine

Example 25A

6-Chloro-9-methyl-8-phenyl-9H-purine

A mixture of trimethyl orthobenzoate (10 mL) and 5-amino-6-chloro-4-methylaminopyrimidine (1.00 g, 6.3 mmol), prepared according to J. Am. Chem. Soc. **79**, 490 (1957), was heated for 72 hours at 150 °C. The cooled solution was concentrated *in vacuo* and the residue purified by flash chromatography on silica gel eluting with ethyl acetate in hexane to afford the title compound as a light yellow solid (980 mg, 64%).

Example 25B

9-Methyl-8-phenyl-6-(N-butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino)-9H-purine

To the compound resulting from Example 2A (2.5 mmol) dissolved in dimethylformamide (3 mL) was added the compound resulting from Example 25A (600 mg, 2.5 mmol) and 4-methylmorpholine (1 mL). The mixture was heated for 27 hours at 65 °C. During the heating, additional portions of the compound resulting from Example 25A (150 mg, 0.6 mmol) were added at 9 hours and 21 hours. Normal work up afforded an orange oil which was purified by flash chromatography on silica gel eluting with ethyl acetate in hexane. Further purification was achieved using flash chromatography eluting with ethyl acetate in methylene chloride to afford the title compound as a colorless amorphous solid (190 mg, 10%).

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Example 25C9-Methyl-8-phenyl-6-[N-butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino]-9H-purine

The compound resulting from Example 25B (170 mg, 0.224 mmol) was deblocked according to the procedure described in Example 10B with the modification that potassium acetate replace potassium carbonate in the neutralization step. The crude product was dissolved in ethyl acetate and treated with hexane to produce the title compound as a colorless solid (66 mg, 57%). ¹H NMR (DMSO-d₆, 300 MHz) δ 0.90 (t, J = 8Hz, 3H), 1.32 (m, 2H), 1.63 (m, 2H), 3.60 (bs, 1H), 3.85 (bs, 1H), 4.20 (s, 3H), 5.03 (bs, 1H), 5.13 (bs, 1H), 7.02 (d, J = 9Hz, 2H), 7.12 (d, J = 9Hz, 2H), 7.50-7.70 (m, 7H), 7.76 (bs, 2H), 8.28 (s, 1H).

Example 265-[2-(4'-N-Propylaminomethyl-biphenyl)]tetrazole hydrochlorideExample 26AN-Benzyloxymethyl-5-(2-bromophenyl)tetrazole

5-(2-Bromophenyl)-[1H]-tetrazole was nitrogen-protected as the benzyloxymethyl (BOM) ether by reaction of a solution of the tetrazole in anhydrous dimethylformamide with technical grade BOM-chloride and anhydrous potassium carbonate. The reaction was complete in less than 60 minutes and the work up involved filtration through Celite and evaporation of the solvent under reduced pressure. The residue obtained was purified by chromatography to afford the title product in 70% yield as an oil which crystallized on standing.

Example 26BN-(4-Bromobenzyl)-N-propylamine

To 4-bromobenzaldehyde (100 g, 0.54 mol) and *n*-propylamine (36.3 g, 0.60 mol) in methanol (100 mL) was added 5% platinum on carbon (1.00 g). This mixture was shaken in a Parr hydrogenation reactor overnight to complete formation of the Schiff base. The reaction was then hydrogenated

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under 4 atmospheres of hydrogen until the theoretical uptake of hydrogen had been consumed. The catalyst was removed by filtration through a 0.45 m nylon frit and washed with methanol. The filtrate was concentrated under reduced pressure and the residue obtained dissolved in ether (500 mL). The ether solution was washed with water (2 x 100 mL), 10% sodium bicarbonate solution (2 x 100 mL), and water (2 x 100 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford the crude title compound (121.34 g). GC-MS showed this material to be 98.5% pure product containing 1.5% of the desbromo compound; the yield is 96.93% based on the GC purity of the product obtained. A sample of this material was purified by bulb-to-bulb distillation (bath temperature 130-150 °C, 0.18 torr). ¹H NMR (CDCl₃, 300 MHz) δ 0.92 (t, J = 7.4 Hz, 3H), 1.36 (bs, 1H), 1.53 (tq, J₁ = J₂ = 7.4 Hz, 2H), 2.57 (t, J = 7.4 Hz, 2H), 3.74 (s, 2H), 7.20 (d, J = 9 Hz, 2H), 7.44 (d, J = 9 Hz, 2H). IR (film) 1430, 1060 cm⁻¹. MS (DCI/NH₃) m/e 228, 230 (M+H)⁺.

Example 26C

4-[(N-*tert*-Butyloxycarbonyl-N-propylamino)methyl]phenyl boronic acid

To the compound resulting from Example 26B in methylene chloride at 0 °C was added triethylamine (2 equivalents) and di-*tert*-butyl-dicarbonate (1.05 equivalents). The cooling bath was removed and the mixture allowed to warm to ambient temperature. The solution was diluted with a suitable solvent (ether or hexane), washed with 2 N hydrochloric acid, dried over sodium sulfate and concentrated *in vacuo*. The Boc-protected compound was obtained as a colorless oil in quantitative yield and was used without further purification.

Grignard formation was effected by treatment of magnesium (1.2 equivalents) in tetrahydrofuran with dibromoethane (0.05 equivalents) followed by heating to reflux and then adding a solution of the protected compound from above in tetrahydrofuran. The reaction mixture turned brown and after 4 hours, most of the metal had been consumed. The Grignard reagent was cooled in a dry ice/acetone bath and then transferred

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via cannula into a -70 °C solution of trimethyl borate (2.5 equivalents) (~2 M in tetrahydrofuran). Upon completion of the addition, the cooling bath was removed and the mixture allowed to warm to ambient temperature. The solution was diluted with ether (4 volumes), washed with 3 N hydrochloric acid, ensuring that the aqueous layer was pH 2 or lower. The pH was then adjusted to 10 by the addition of 1 N sodium hydroxide and the ether layer was discarded. The aqueous solution was cooled to 0 °C, carefully acidified to pH 2 with 3 N hydrochloric acid and extracted with ether. The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to about 20% of volume whereupon the boronic acid crystallizes in 36% yield.

Example 26D

N-Benzylloxymethyl-5-[2-[4'-(N-propyl-N-tert-butylloxycarbonylamino)methyl-biphenyl]]tetrazole

To palladium tetrakis(triphenylphosphine) (0.05 equivalents) dissolved in toluene was added a solution of the compound resulting from Example 26A (1 equivalent). After 10 minutes, a 2 M aqueous solution of sodium carbonate was added followed by the compound resulting from Example 26C dissolved in the minimum amount of ethanol. The two-phase mixture was rapidly stirred under reflux for 2.5 hours and then cooled to ambient temperature. The solution was diluted with ether and the organic phase was dried over sodium sulfate and concentrated *in vacuo* to afford a brown oil. Filtration through silica gel eluting with 35% ether in hexanes afforded the title compound as a colorless oil (87%).

Example 26E

5-[2-(4'-N-Propylaminomethyl-biphenyl)]tetrazole hydrochloride

To the compound resulting from Example 26D (1.00 g, 1.94 mmol) dissolved in 1 mL of absolute ethanol at ambient temperature was added a solution of anhydrous hydrogen chloride (g) dissolved in ethanol (5 mL, 11.2 M). There was observed an immediate evolution of carbon dioxide

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which lasted about 90 minutes; also during this time a heavy white precipitate appeared. After 3 hours, the solvent was removed *in vacuo* and the residue triturated with 8 mL of ethyl acetate. The white solid was then dried *in vacuo* at 60 °C to afford the title compound (553 mg, 86%).

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. Pharmaceutically acceptable salts are described in Berge, et al., J. Pharmaceutical Sciences 66 1-19 (1977). These salts include but are not limited to the following: acetate, adipate, alginate, citrate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, phosphate, 3-phenylpropionate, picrate, pivalate, propionate, stearate, succinate, tartrate, thiocyanate, toluenesulfonate (tosylate), undecanoate and valerate.

Examples of acids which can be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid, methanesulfonic acid and citric acid. Other salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases. The salts can be prepared *in situ* during the final isolation and purification of the compounds of formula (I), or separately by reacting the free base function with a suitable acid or by reacting the acidic function with a suitable base.

The compounds of the present invention are useful for blocking the interaction of angiotensin II with angiotensin II receptors and for treating hypertension, edema, renal failure, congestive heart failure, glaucoma, psoriasis, benign prostatic hypertrophy, diabetic nephropathy, diabetic

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retinopathy, or to prevent atherosclerosis or for treating gastrointestinal disorders associated with enhanced contractility and/or motility of intestinal smooth muscle or for treating contractile disorders of the uterus (including premature contractions, dysmenorrhea and the like) or for treating or preventing stroke, cerebral vasospasm or cerebral infarction or for treating CNS disorders (depression, schizophrenia, anxiety or cognitive disorders (Alzheimer's disease, amnesia and senile dementia)) in a human or other mammal. The compounds of the invention are also useful for enhancing intimal wound closure and for reducing luminal thrombogenicity in a human or other mammal.

The ability of the compounds of the invention to block the interaction of angiotensin II with angiotensin II receptors can be demonstrated as described below.

ANGIOTENSIN II FUNCTIONAL ASSAY: Antagonism of Contraction of Rabbit Aorta

The protocol reported by A.T Chiu and P.Timmermans (P.C. Wong, *et al. Hypertension*, **13**, 489-497 (1989)) was followed with a few modifications. Female New Zealand White rabbits weighing 2-5 kg were sedated with carbon dioxide and then sacrificed. Main abdominal aortas were removed and placed in Krebs-Henseleit buffer at room temperature.

Krebs-Henseleit buffer

| <u>Buffer Component</u> | <u>mM Concentration</u> |
|--------------------------------|--------------------------------|
| sodium chloride | 119.00 |
| potassium chloride | 4.70 |
| potassium dihydrogen phosphate | 1.20 |
| calcium chloride | 2.50 |
| sodium bicarbonate | 20.00 |
| magnesium sulfate | 1.50 |
| dextrose | 11.00 |
| EDTA* disodium calcium salt | 0.01 |

* EDTA = ethylenediamine tetraacetic acid

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The buffer contained no cocaine, propranolol or steroid.

The pH of the buffer was 7.40 at 37°C when saturated with 5% carbon dioxide/95% oxygen.

The tissues were cleaned of extraneous connective tissue, cut into 3 mm rings, and suspended within a 10 mL tissue bath. All dilutions of peptide preparations were made with 0.3% aqueous BSA. The tissues were primed with 55 mM potassium chloride. Tissues were pre-loaded with 1 g of tension. Tension was recorded on a model 7 Grass polygraph using FT03 transducers. At the end of the equilibrium period, a control cumulative concentration-contractile response curve for angiotensin II (A II: 1×10^{-10} - 10^{-8} M) was obtained. The tissue was washed several times until the baseline was reached. Forty five minutes later, test compound (antagonist) was added and the tissue was incubated for 30 minutes. The concentration-response curve for A II was then repeated in the presence of the test compound. One dose of antagonist was tested per tissue only. For single dose shift experiments a dose of 1 mM of test compound was used, for a full pA₂ experiment multiple doses were used depending upon the potency of the antagonist.

All responses to the control agonist were calculated as a percentage of the maximum response. These points in duplicate were plotted and analyzed according to standard Schild analysis (H.O. Schild, *British J Pharmacology and Chemotherapy*, 2, 189-206 (1947)). The pA₂ values calculated for the compounds of the invention are shown in Table 1. The pA₂ value is the negative logarithm of the [A]₂ value. [A]₂ is the concentration of antagonist which necessitates doubling the agonist concentration in order to achieve the agonist effect which was measured in the absence of antagonist.

The pA₂ value, therefore is a measure of the effectiveness of the compound as an antagonist. The data in Table 1 show that the compounds of the invention are potent antagonists at the angiotensin II receptor.

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Table 1: pA₂ Values from Isolated Rabbit Aorta Assay

| <u>Example</u> | <u>pA₂</u> |
|----------------------------|-----------------------|
| 2 | 8.08 |
| 3 | 8.17 |
| 5 | 7.92 |
| 10 | 8.81 |
| 11 | 7.97 |
| 13 | 8.14 |
| Sar,-1, Thr-8 All (SARILE) | 9.02 |

The ability of the compounds of the invention to lower blood pressure in vivo in renal artery ligated rats can be demonstrated according to the method disclosed by Cangiano, et al., J. Pharmacol. Exp. Ther. 208 310 (1979)).

The total daily dose of the compounds of this invention administered to a human or other mammal in single or in divided doses can be in amounts, for example, from 0.01 to 25 mg/kg body weight or more usually from 0.1 to 15 mg/kg body weight. Single dose compositions can contain such amounts or submultiples thereof to make up the daily dose. In general, treatment regimens according to the present invention comprise administration to a patient in need of such treatment from about 10 mg to about 1000 mg of the compound(s) of this invention per day in multiple doses or in a single dose of from 10 mg to 1000 mg.

It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgement. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the

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time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

The compounds of the present invention can be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration can also involve the use of transdermal administration such as transdermal patches. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art such as water. Such compositions can also comprise adjuvants, such as wetting agents; emulsifying and suspending agents; sweetening, flavoring and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

The injectable formulation can be sterilized, for example, by filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

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In order to prolong the effect of a drug, it is often desirable to slow the absorption of a drug from subcutaneous or intramuscular injection. The most common way to accomplish this is to inject a suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug becomes dependent on the rate of dissolution of the drug which is, in turn, dependent on the physical state of the drug, for example, the crystal size and the crystalline form. Another approach to delaying absorption of a drug is to administer the drug as a solution or suspension in oil. Injectable depot forms can also be made by forming microcapsule matrices of drugs and biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer and the composition of the polymer, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly-orthoesters and polyanhydrides. The depot injectables can also be made by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycol which are solid at ordinary temperature but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration can include capsules, tablets, pills, powders, prills and granules. In such solid dosage forms the active compound can be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms can also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings and other release-controlling coatings.

Solid compositions of a similar type can also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

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The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They can optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferably, in a certain part of the intestinal tract, optionally in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as can be required. Ophthalmic formulations, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels can contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

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Some examples of the materials that can serve as pharmaceutically acceptable carriers are sugars, such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols such as glycerin, sorbitol, mannitol and polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol and phosphate buffer solutions, as well as other non-toxic compatible substances used in pharmaceutical formulations. Wetting agents, emulsifiers and lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgement of the formulator.

The compounds of the present invention can be administered alone or in combination or in concurrent therapy with other cardiovascular agents independently selected from diuretics, adrenergic blocking agents, vasodilators, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, potassium channel activators, antiserotonergic agents, thromboxane synthetase inhibitors, renin inhibitors and other agents useful for treating (in a human or other mammal) hypertension, edema or congestive heart failure.

Representative diuretics include hydrochlorothiazide, chlorothiazide, acetazolamide, amiloride, bumetanide, benzthiazide, ethacrynic acid, furosemide, indacrinone, metolazone, spironolactone, triamterene, chlorthalidone and the like or a pharmaceutically acceptable salt thereof.

Representative adrenergic blocking agents include phentolamine, phenoxybenzamine, prazosin, terazosin, tolazine, atenolol, metoprolol, nadolol,

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propranolol, timolol, carteolol and the like or a pharmaceutically acceptable salt thereof.

Representative vasodilators include hydralazine, minoxidil, diazoxide, nitroprusside, flosequinan and the like or a pharmaceutically acceptable salt thereof.

Representative calcium channel blockers include amrinone, bencyclane, diltiazem, fendiline, flunarizine, nifedipine, nimodipine, perhexilene, verapamil, gallopamil, nifedipine and the like or a pharmaceutically acceptable salt thereof.

Representative ACE inhibitors include captopril, enalapril, lisinopril and the like or a pharmaceutically acceptable salt thereof.

Representative potassium channel activators include pinacidil and the like or a pharmaceutically acceptable salt thereof.

Representative antiserotonergic agents include ketanserin and the like or a pharmaceutically acceptable salt thereof.

Representative renin inhibitors include enalkiren, A-72517, PD-134672 or Ro 42-5892 and the like or a pharmaceutically acceptable salt thereof.

Other representative cardiovascular agents include sympatholytic agents such as methyldopa, clonidine, guanabenz, reserpine and the like or a pharmaceutically acceptable salt thereof.

The compound of formula I and the other cardiovascular agent can be administered at the recommended maximum clinical dosage or at lower doses. Dosage levels of the active compounds in the compositions of the invention can be varied so as to obtain a desired therapeutic response depending on the route of administration, severity of the disease and the response of the patient. The combination can be administered as separate compositions or as a single dosage form containing both agents.

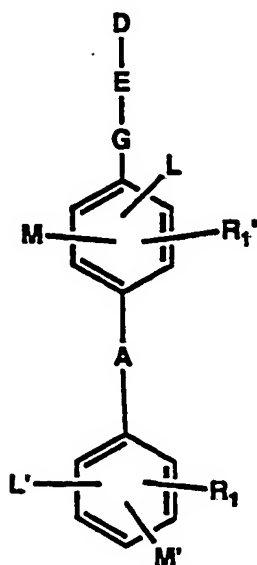
The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

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CLAIMS

What is claimed is:

1. A compound of the formula:



wherein

A is

- (i) a covalent bond,
- (ii) -O-,
- (iii) -C(O)-,
- (iv) -CH₂-,
- (v) -S-, -S(O)- or -S(O)₂-;

E-G is

- (i) -N(R₅)-,
- (ii) -O-,

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- (iii) -S-,
- (iv) -N(R₅)-CH(R₅)-,
- (v) -O-CH(R₅)-,
- (vi) -S-CH(R₅)-,
- (vii) -C(R₅') (R₅)-CH(R₅)-,
- (viii) -CH(R₅)-C(R₅') (R₅)-,
- (ix) -CH(R₅)-N(R₅)-,
- (x) -CH(R₅)-O-,
- (xi) -CH(R₅)-S-,
- (xii) -N(R₅)-N(R₅)-,
- (xiii) -C(R₅)=C(R₅)- or
- (xiv) -CH(R₅)-C(R₅') (R₅)-N(R₅)- wherein at each occurrence R₅ is independently selected from hydrogen, loweralkyl, alkoxy-substituted loweralkyl, halo-substituted loweralkyl, carboxy-substituted loweralkyl, heterocyclic-substituted loweralkyl, alkenyl, alkynyl, cycloalkyl or cycloalkylalkyl and R₅' is hydrogen, halo, hydroxy, carboxy, alkoxy or thioalkoxy;

L, L', M and M' are independently selected from

- (i) hydrogen,
- (ii) loweralkyl,
- (iii) halo-substituted loweralkyl,
- (iv) halo,
- (v) -CN,
- (vi) -NO₂,
- (vii) -OH,
- (viii) hydroxy-substituted loweralkyl,
- (ix) alkoxy-substituted loweralkyl,
- (x) -NH₂,
- (xi) alkylamino,
- (xii) dialkylamino,
- (xiii) -SH,

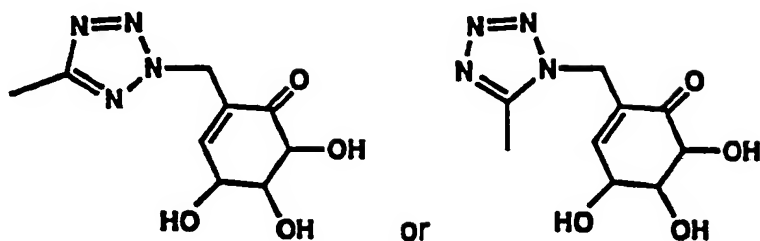
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- (xiv) alkoxy and
(xv) thioalkoxy;

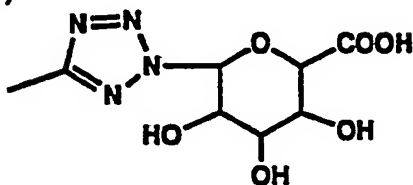
R_1 and R_1' are independently selected from

(i) tetrazolyl,

(ii)



(iii)



(iv) $-NH-C(=N(R_{50a}))(R_{51a})$ wherein R_{50a} is hydrogen, $-CN$ or $-NO_2$ and R_{51a} is hydrogen, loweralkyl, alkylamino, dialkylamino, alkoxy or thioalkoxy,

(v) $-NH(R_{51b})$ wherein R_{51b} is a 5-membered aromatic heterocyclic ring wherein the heterocyclic ring contains 1, 2, 3 or 4 nitrogen atoms or 1 nitrogen atom and 1 oxygen atom or 2 nitrogen atoms and 1 oxygen atom or 1 oxygen atom and 1 sulfur atom and wherein the 5-membered heterocyclic ring is unsubstituted or substituted with a substituent selected from amino, alkylamino, dialkylamino, hydroxy, alkoxy, thioalkoxy, halo, loweralkyl and halo-substituted loweralkyl,

(vi) $-COOR_6$ or $-CH_2COOR_6$ wherein R_6 is hydrogen or a carboxy-protecting group or

(vii) $-NHS(O)_2R_7$ or $-CH_2NHS(O)_2R_7$ or $-NHC(O)R_{7a}$ or

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- CH₂NHC(O)R_{7a} wherein R₇ is loweralkyl, halo-substituted loweralkyl or -NR_{7b}R_{7c} wherein R_{7b} and R_{7c} are independently selected from hydrogen and loweralkyl and R_{7a} is loweralkyl, halo-substituted loweralkyl, amino, alkylamino, dialkylamino or -COOH;
- (viii) -C(O)NR₅₀R₅₁ or -CH₂C(O)NR₅₀R₅₁ or -NHC(O)NR₅₀R₅₁ or -CH₂NHC(O)NR₅₀R₅₁ or -NHC(S)NR₅₀R₅₁ or -CH₂NHC(S)NR₅₀R₅₁ wherein R₅₀ and R₅₁ are independently selected from hydrogen, loweralkyl, hydroxy, alkoxy, hydroxy-substituted loweralkyl, alkoxy-substituted loweralkyl, alkoxy-substituted alkoxy and -S(O)₂R_{50a} wherein R_{50a} is loweralkyl or aryl, or R₅₀ and R₅₁ taken together with the nitrogen atom to which they are attached form a 5- to 7-membered aliphatic heterocycle;
- (ix) -CH₂OR₅₂ wherein R₅₂ is selected from hydrogen, loweralkyl and -C(O)R₅₃ wherein R₅₃ is hydrogen, loweralkyl or aryl;
- (x) -CH(OH)R_{52a} or -C(O)R_{52a} wherein R_{52a} is loweralkyl, halo-substituted loweralkyl, -CF₂COOR_{53a} or -CH₂COOR_{53a} wherein R_{53a} is hydrogen or a carboxy-protecting group,
- (xii) -CH₂NR₅₄R₅₅ wherein R₅₄ is selected from hydrogen, loweralkyl, -C(O)R₅₆, -C(O)NR₅₆R₅₇ and -S(O)₂R₅₈ wherein R₅₆ is selected from hydrogen, loweralkyl and aryl and R₅₈ is selected from lower alkyl and halo-substituted loweralkyl and wherein R₅₅ and R₅₇ are independently selected from hydrogen, loweralkyl, hydroxy and alkoxy;
- (xiii) -SO₃H, -OSO₃H or -CH₂SO₃H,
- (xiv) -OPO₃H₂, -PO₃H₂ or -CH₂PO₃H₂,
- (xv) -SO₂NR₅₀R₅₁ or -CH₂SO₂NR₅₀R₅₁ wherein R₅₀ and R₅₁ are defined as above and
- (xvi) -C(O)NHSO₂R₆₀, -C(O)NHC(O)R₆₀ or -C(O)NHNHSO₂R₆₀ wherein R₆₀ is loweralkyl, halo-substituted loweralkyl or aryl;
- with the proviso that one of R₁ and R₁' is hydrogen, but R₁ and R₁' are not both hydrogen;
- and

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D is

(i) a bicyclic heterocycle comprising a 6-membered ring fused to a 5-membered ring, the bicyclic heterocycle comprising at least one heteroatom selected from N, O and S; the 6-membered ring of the bicyclic heterocycle comprising 0, 1, 2 or 3 nitrogen atoms or 1 nitrogen atom and 1 oxygen atom or 1 nitrogen atom and 1 sulfur atom or 1 oxygen atom and 1 sulfur atom or 2 oxygen atoms or 2 sulfur atoms or 1 oxygen atom or 1 sulfur atom, the remaining ring atoms being carbon atoms and the 6-membered ring comprising 0, 1, 2 or 3 double bonds; the 5-membered ring of the bicyclic heterocycle comprising 0, 1, 2 or 3 nitrogen atoms or 1 nitrogen and 1 oxygen atom or 1 nitrogen and 1 sulfur atom or 1 oxygen atom and 1 sulfur atom or 1 sulfur atom or 1 oxygen atom, the remaining ring atoms being carbon atoms and the 5-membered ring comprising 0, 1 or 2 double bonds; the nitrogen atoms of the bicyclic heterocycle can be substituted with a substituent R_2 wherein at each occurrence R_2 is independently selected from hydrogen, loweralkyl, carboxy-substituted loweralkyl or alkoxycarbonyl-substituted loweralkyl; the nitrogen atoms of the bicyclic heterocycle can be oxidized; one or two carbon atoms of the bicyclic heterocycle can be substituted with an oxo ($=O$) substituent and the sulfur atoms of the bicyclic heterocycle can be substituted with one or two oxo ($=O$) substituents; the bicyclic heterocycle can be substituted with one, two or three substituents independently selected from R_3 and R_4 , R_3 being bonded to a carbon atom or a nitrogen atom of the bicyclic heterocycle and R_4 being bonded to a carbon atom or a nitrogen atom of the bicyclic heterocycle, wherein

R_3 is

- (i) hydrogen,
- (ii) loweralkyl,
- (iii) halo,
- (iv) halo-substituted loweralkyl,
- (v) thioalkoxy,

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- (vi) alkoxy-substituted loweralkyl,
- (vii) thioalkoxy-substituted loweralkyl,
- (viii) aryl,
- (ix) arylalkyl,
- (x) -NO₂,
- (xi) -COOR₈ wherein R₈ is hydrogen or a carboxy-protecting group,
- (xii) -OR₉ wherein R₉ is hydrogen, loweralkyl, halo-substituted loweralkyl, aryl, arylalkyl, heterocyclic-substituted loweralkyl or -C(O)R₁₀ wherein R₁₀ is loweralkyl, halo-substituted loweralkyl, -PO₃H₂ or -NR₁₁R₁₂ wherein R₁₁ and R₁₂ are independently selected from hydrogen and loweralkyl and
- (xiii) -NR₁₃R₁₄ or -CH₂NR₁₃R₁₄ wherein R₁₃ and R₁₄ are independently selected from (1) hydrogen, (2) lower alkyl, (3) arylalkyl, (4) -C(O)R₁₅, (5) -S(O)₂R₁₅ wherein R₁₅ is loweralkyl or halo-substituted loweralkyl and (6) -R₁₆-R₁₇ wherein R₁₆ is alkylene and R₁₇ is
 - (a) -NR₁₈R₁₉ wherein R₁₈ and R₁₉ are independently selected from hydrogen and loweralkyl or
 - (b) unsubstituted or loweralkyl substituted aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyridinyl or pyrimidinyl, or R₁₃ and R₁₄ taken together with the nitrogen atom to which they are attached form a 5- to 7-membered aliphatic heterocycle and

R₄ is

- (i) hydrogen,
- (ii) loweralkyl,
- (iii) halo-substituted loweralkyl,
- (iv) -CN,
- (v) -NO₂,
- (vi) -NH₂,

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- (vii) $-\text{NH}-\text{C}(=\text{N}(\text{R}_{25a}))(\text{R}_{26a})$ wherein R_{25a} is hydrogen, $-\text{CN}$ or $-\text{NO}_2$ and R_{26a} is hydrogen, loweralkyl, alkylamino, dialkylamino, alkoxy or thioalkoxy,
- (viii) $-\text{NH}(\text{R}_{26b})$ wherein R_{26b} is a 5-membered aromatic heterocyclic ring wherein the heterocyclic ring contains 1, 2, 3 or 4 nitrogen atoms or 1 nitrogen atom and 1 oxygen atom or 2 nitrogen atoms and 1 oxygen atom or 1 oxygen atom and 1 sulfur atom and wherein the 5-membered heterocyclic ring is unsubstituted or substituted with a substituent selected from amino, alkylamino, dialkylamino, hydroxy, alkoxy, thioalkoxy, halo, loweralkyl and halo-substituted loweralkyl,
- (ix) $-\text{CHO}$ or $-\text{CH}(=\text{N}-\text{OH})$,
- (x) tetrazolyl,
- (xi) $-\text{NHS}(\text{O})_2\text{R}_{20}$ or $-\text{CH}_2\text{NHS}(\text{O})_2\text{R}_{20}$ or $-\text{NHC}(\text{O})\text{R}_{21}$ or $-\text{N}(\text{OH})\text{C}(\text{O})\text{R}_{21}$ or $-\text{CH}_2\text{NHC}(\text{O})\text{R}_{21}$ or $-\text{CH}_2\text{N}(\text{OH})\text{C}(\text{O})\text{R}_{21}$ wherein R_{20} is loweralkyl, halo-substituted loweralkyl or $-\text{NR}_{27a}\text{R}_{27b}$ wherein R_{27a} and R_{27b} are independently selected from hydrogen, $-\text{OH}$ and loweralkyl and R_{21} is loweralkyl, halo-substituted loweralkyl, amino, alkylamino, dialkylamino or $-\text{COOH}$,
- (xii) $-\text{CH}(\text{OH})\text{R}_{22}$ or $-\text{C}(\text{O})\text{R}_{22}$ wherein R_{22} is loweralkyl, halo-substituted loweralkyl, $-\text{CF}_2\text{COOR}_{23}$ or $-\text{CH}_2\text{COOR}_{23}$ wherein R_{23} is hydrogen or a carboxy-protecting group,
- (xiii) $-\text{COOR}_{24}$ or $-\text{CH}_2\text{COOR}_{24}$ wherein R_{24} is hydrogen or a carboxy-protecting group,
- (xiv) $-\text{C}(\text{O})\text{NR}_{25}\text{R}_{26}$ or $-\text{CH}_2\text{C}(\text{O})\text{NR}_{25}\text{R}_{26}$ or $-\text{NHC}(\text{O})\text{NR}_{25}\text{R}_{26}$ or $-\text{CH}_2\text{NHC}(\text{O})\text{NR}_{25}\text{R}_{26}$ or $-\text{NHC}(\text{S})\text{NR}_{25}\text{R}_{26}$ or $-\text{CH}_2\text{NHC}(\text{S})\text{NR}_{25}\text{R}_{26}$ wherein R_{25} and R_{26} are independently selected from hydrogen, loweralkyl, hydroxy, alkoxy, hydroxy-substituted loweralkyl, alkoxy-substituted loweralkyl, alkoxy-substituted alkoxy and $-\text{S}(\text{O})_2\text{R}_{28a}$ wherein R_{28a} is loweralkyl or aryl, or R_{25} and R_{26} taken together with the nitrogen atom to which they are attached form a 5- to 7- membered aliphatic heterocycle;

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- (xv) $-\text{CH}_2\text{OR}_{27}$ wherein R_{27} is selected from hydrogen, loweralkyl and $-\text{C}(\text{O})\text{R}_{28}$ wherein R_{28} is hydrogen, loweralkyl or aryl;
- (xvi) $-\text{CH}_2\text{NR}_{29}\text{R}_{30}$ wherein R_{29} is selected from hydrogen, loweralkyl, $-\text{C}(\text{O})\text{R}_{31}$, $-\text{C}(\text{O})\text{NR}_{31}\text{R}_{32}$ and $-\text{S}(\text{O})_2\text{R}_{33}$ wherein R_{31} is selected from hydrogen, loweralkyl and aryl and R_{33} is selected from loweralkyl and halo-substituted loweralkyl and wherein R_{30} and R_{32} are independently selected from hydrogen, loweralkyl, hydroxy and alkoxy;
- (xvii) $-\text{SO}_3\text{H}$, $-\text{OSO}_3\text{H}$ or $-\text{CH}_2\text{SO}_3\text{H}$,
- (xviii) $-\text{OPO}_3\text{H}$, $-\text{PO}_3\text{H}_2$ or $-\text{CH}_2\text{PO}_3\text{H}_2$,
- (xix) $-\text{SO}_2\text{NR}_{25}\text{R}_{26}$ or $-\text{CH}_2\text{SO}_2\text{NR}_{25}\text{R}_{26}$ wherein R_{25} and R_{26} are defined as above and
- (xx) $-\text{C}(\text{O})\text{NHSO}_2\text{R}_{59}$, $-\text{C}(\text{O})\text{NHC}(\text{O})\text{R}_{59}$ or $-\text{C}(\text{O})\text{NHNHSO}_2\text{R}_{59}$ wherein R_{59} is loweralkyl, halo-substituted loweralkyl or aryl;

or D is

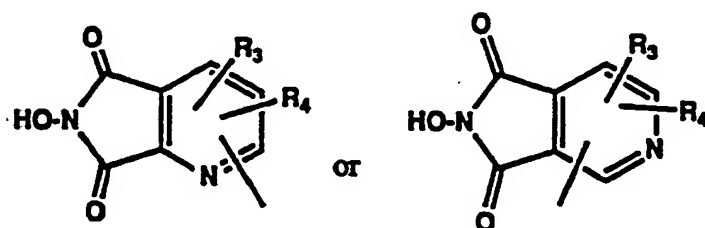
(ii) a bicyclic heterocycle comprising a 5-membered ring fused to a 5-membered ring, the bicyclic heterocycle comprising at least one heteroatom selected from N, O and S; each of the 5-membered rings of the bicyclic heterocycle independently comprising 0, 1, 2 or 3 nitrogen atoms or 1 nitrogen and 1 oxygen atom or 1 nitrogen and 1 sulfur atom or 1 oxygen atom and 1 sulfur atom or 1 sulfur atom or 1 oxygen atom, the remaining ring atoms being carbon atoms and each of the 5-membered rings independently comprising 0, 1 or 2 double bonds; the nitrogen atoms of the bicyclic heterocycle can be substituted with a substituent R_2 wherein at each occurrence R_2 is independently selected from hydrogen, loweralkyl, carboxy-substituted loweralkyl or alkoxycarbonyl-substituted loweralkyl; the nitrogen atoms of the bicyclic heterocycle can be oxidized; one or two carbon atoms of the bicyclic heterocycle can be substituted with an oxo ($=\text{O}$)

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substituent and the sulfur atoms of the bicyclic heterocycle can be substituted with one or two oxo (=O) substituents; the bicyclic heterocycle can be substituted with one or two substituents independently selected from R_3 and R_4 , R_3 being bonded to a carbon atom or a nitrogen atom of the bicyclic heterocycle and R_4 being bonded to a carbon atom or a nitrogen atom of the bicyclic heterocycle, wherein R_3 and R_4 are defined as above;

or D is

(iii)

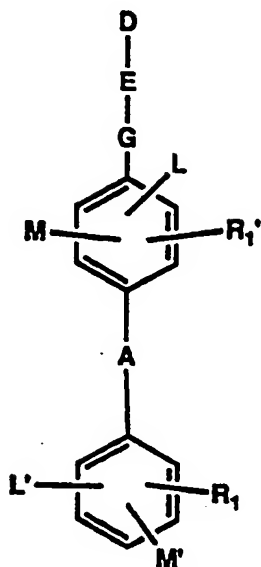


wherein R_3 and R_4 are defined as above;
or a pharmaceutically acceptable salt or prodrug thereof.

2. The compound of Claim 1 wherein A is a covalent bond, L, L', M, M' and R_1' are hydrogen, -G-E- is $-\text{CH}_2-\text{N}(\text{R}_5)-$ and D is a substituted purinyl group.

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3. A compound of the formula:



wherein

A is

- (i) a covalent bond,
- (ii) -O-,
- (iii) -C(O)-,
- (iv) -CH₂-,
- (v) -S-, -S(O)- or -S(O)₂-;

E-G is

- (i) -N(R₅)-,
- (ii) -O-,
- (iii) -S-,
- (iv) -N(R₅)-CH(R₅)-,
- (v) -O-CH(R₅)-,
- (vi) -S-CH(R₅)-,
- (vii) -C(R₅') (R₅)-CH(R₅)-,

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- (viii) $-\text{CH}(\text{R}_5)-\text{C}(\text{R}_5')(\text{R}_5)-$,
- (ix) $-\text{CH}(\text{R}_5)-\text{N}(\text{R}_5)-$,
- (x) $-\text{CH}(\text{R}_5)-\text{O}-$,
- (xi) $-\text{CH}(\text{R}_5)-\text{S}-$,
- (xii) $-\text{N}(\text{R}_5)-\text{N}(\text{R}_5)-$,
- (xiii) $-\text{C}(\text{R}_5)=\text{C}(\text{R}_5)-$ or
- (xiv) $-\text{CH}(\text{R}_5)-\text{C}(\text{R}_5')(\text{R}_5)-\text{N}(\text{R}_5)-$ wherein at each occurrence R_5 is independently selected from hydrogen, loweralkyl, alkoxy-substituted loweralkyl, halo-substituted loweralkyl, carboxy-substituted loweralkyl, heterocyclic-substituted loweralkyl, alkenyl, alkynyl, cycloalkyl or cycloalkylalkyl and R_5' is hydrogen, halo, hydroxy, carboxy, alkoxy or thioalkoxy;

L, L', M and M' are independently selected from

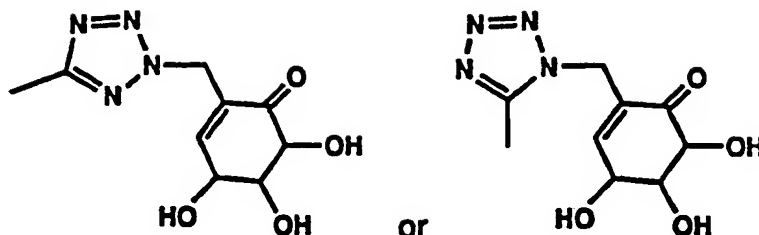
- (i) hydrogen,
- (ii) loweralkyl,
- (iii) halo-substituted loweralkyl,
- (iv) halo,
- (v) $-\text{CN}$,
- (vi) $-\text{NO}_2$,
- (vii) $-\text{OH}$,
- (viii) hydroxy-substituted loweralkyl,
- (ix) alkoxy-substituted loweralkyl,
- (x) $-\text{NH}_2$,
- (xi) alkylamino,
- (xii) dialkylamino,
- (xiii) $-\text{SH}$,
- (xiv) alkoxy and
- (xv) thioalkoxy;

R_1 and R_1' are independently selected from

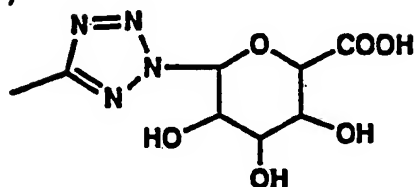
- (i) tetrazolyl,

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(ii)



(iii)



(iv) $\text{-NH-C(=N(R}_{50\text{a}))R}_{51\text{a}}$ wherein $\text{R}_{50\text{a}}$ is hydrogen, -CN or -NO_2 and $\text{R}_{51\text{a}}$ is hydrogen, loweralkyl, alkylamino, dialkylamino, alkoxy or thioalkoxy,

(v) $\text{-NH(R}_{51\text{b}})$ wherein $\text{R}_{51\text{b}}$ is a 5-membered aromatic heterocyclic ring wherein the heterocyclic ring contains 1, 2, 3 or 4 nitrogen atoms or 1 nitrogen atom and 1 oxygen atom or 2 nitrogen atoms and 1 oxygen atom or 1 oxygen atom and 1 sulfur atom and wherein the 5-membered heterocyclic ring is unsubstituted or substituted with a substituent selected from amino, alkylamino, dialkylamino, hydroxy, alkoxy, thioalkoxy, halo, loweralkyl and halo-substituted loweralkyl,

(vi) -COOR_6 or $\text{-CH}_2\text{COOR}_6$ wherein R_6 is hydrogen or a carboxy-protecting group or

(vii) $\text{-NHS(O)}_2\text{R}_7$ or $\text{-CH}_2\text{NHS(O)}_2\text{R}_7$ or $\text{-NHC(O)R}_{7\text{a}}$ or $\text{-CH}_2\text{NHC(O)R}_{7\text{a}}$ wherein R_7 is loweralkyl, halo-substituted loweralkyl or $\text{-NR}_{7\text{b}}\text{R}_{7\text{c}}$ wherein $\text{R}_{7\text{b}}$ and $\text{R}_{7\text{c}}$ are independently selected from hydrogen and loweralkyl and $\text{R}_{7\text{a}}$ is loweralkyl, halo-substituted loweralkyl, amino, alkylamino, dialkylamino or -COOH ;

(viii) $\text{-C(O)NR}_{50}\text{R}_{51}$ or $\text{-CH}_2\text{C(O)NR}_{50}\text{R}_{51}$ or $\text{-NHC(O)NR}_{50}\text{R}_{51}$

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- or $-\text{CH}_2\text{NHC}(\text{O})\text{NR}_{50}\text{R}_{51}$ or $-\text{NHC}(\text{S})\text{NR}_{50}\text{R}_{51}$ or $-\text{CH}_2\text{NHC}(\text{S})\text{NR}_{50}\text{R}_{51}$ wherein R_{50} and R_{51} are independently selected from hydrogen, loweralkyl, hydroxy, alkoxy, hydroxy-substituted loweralkyl, alkoxy-substituted loweralkyl, alkoxy-substituted alkoxy and $-\text{S}(\text{O})_2\text{R}_{50a}$ wherein R_{50a} is loweralkyl or aryl, or R_{50} and R_{51} taken together with the nitrogen atom to which they are attached form a 5- to 7-membered aliphatic heterocycle;
- (ix) $-\text{CH}_2\text{OR}_{52}$ wherein R_{52} is selected from hydrogen, loweralkyl and $-\text{C}(\text{O})\text{R}_{53}$ wherein R_{53} is hydrogen, loweralkyl or aryl;
- (x) $-\text{CH}(\text{OH})\text{R}_{52a}$ or $-\text{C}(\text{O})\text{R}_{52a}$ wherein R_{52a} is loweralkyl, halo-substituted loweralkyl, $-\text{CF}_2\text{COOR}_{53a}$ or $-\text{CH}_2\text{COOR}_{53a}$ wherein R_{53a} is hydrogen or a carboxy-protecting group,
- (xii) $-\text{CH}_2\text{NR}_{54}\text{R}_{55}$ wherein R_{54} is selected from hydrogen, loweralkyl, $-\text{C}(\text{O})\text{R}_{56}$, $-\text{C}(\text{O})\text{NR}_{56}\text{R}_{57}$ and $-\text{S}(\text{O})_2\text{R}_{58}$ wherein R_{56} is selected from hydrogen, loweralkyl and aryl and R_{58} is selected from lower alkyl and halo-substituted loweralkyl and wherein R_{55} and R_{57} are independently selected from hydrogen, loweralkyl, hydroxy and alkoxy;
- (xiii) $-\text{SO}_3\text{H}$, $-\text{OSO}_3\text{H}$ or $-\text{CH}_2\text{SO}_3\text{H}$,
- (xiv) $-\text{OPO}_3\text{H}_2$, $-\text{PO}_3\text{H}_2$ or $-\text{CH}_2\text{PO}_3\text{H}_2$,
- (xv) $-\text{SO}_2\text{NR}_{50}\text{R}_{51}$ or $-\text{CH}_2\text{SO}_2\text{NR}_{50}\text{R}_{51}$ wherein R_{50} and R_{51} are defined as above and
- (xvi) $-\text{C}(\text{O})\text{NHSO}_2\text{R}_{60}$, $-\text{C}(\text{O})\text{NHC}(\text{O})\text{R}_{60}$ or $-\text{C}(\text{O})\text{NHNHSO}_2\text{R}_{60}$ wherein R_{60} is loweralkyl, halo-substituted loweralkyl or aryl;

with the proviso that one of R_1 and $\text{R}_{1'}$ is hydrogen, but R_1 and $\text{R}_{1'}$ are not both hydrogen;
and

D is

- (i) a bicyclic heterocycle comprising a 6-membered ring fused to a 5-membered ring, the bicyclic heterocycle comprising at least one heteroatom selected from N, O and S; the 6-membered ring of the bicyclic

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heterocycle comprising 0, 1, 2 or 3 nitrogen atoms or 1 nitrogen atom and 1 oxygen atom or 1 nitrogen atom and 1 sulfur atom or 1 oxygen atom and 1 sulfur atom or 2 oxygen atoms or 2 sulfur atoms or 1 oxygen atom or 1 sulfur atom, the remaining ring atoms being carbon atoms and the 6-membered ring comprising 0, 1, 2 or 3 double bonds; the 5-membered ring of the bicyclic heterocycle comprising 0, 1, 2 or 3 nitrogen atoms or 1 nitrogen and 1 oxygen atom or 1 nitrogen and 1 sulfur atom or 1 oxygen atom and 1 sulfur atom or 1 sulfur atom or 1 oxygen atom, the remaining ring atoms being carbon atoms and the 5-membered ring comprising 0, 1 or 2 double bonds; the nitrogen atoms of the bicyclic heterocycle can be substituted with a substituent R_2 wherein at each occurrence R_2 is independently selected from hydrogen, loweralkyl, carboxy-substituted loweralkyl or alkoxycarbonyl-substituted loweralkyl; the nitrogen atoms of the bicyclic heterocycle can be oxidized; one or two carbon atoms of the bicyclic heterocycle can be substituted with an oxo (=O) substituent and the sulfur atoms of the bicyclic heterocycle can be substituted with one or two oxo (=O) substituents; the bicyclic heterocycle can be substituted with one, two or three substituents independently selected from R_3 and R_4 , R_3 being bonded to a carbon atom or a nitrogen atom of the bicyclic heterocycle and R_4 being bonded to a carbon atom or a nitrogen atom of the bicyclic heterocycle, wherein

R_3 is

- (i) hydrogen,
- (ii) loweralkyl,
- (iii) halo,
- (iv) halo-substituted loweralkyl,
- (v) thioalkoxy,
- (vi) alkoxy-substituted loweralkyl,
- (vii) thioalkoxy-substituted loweralkyl,
- (viii) aryl,
- (ix) arylalkyl,
- (x) $-NO_2$,

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- (xi) $-\text{COOR}_8$ wherein R_8 is hydrogen or a carboxy-protecting group,
- (xii) $-\text{OR}_9$ wherein R_9 is hydrogen, loweralkyl, halo-substituted loweralkyl, aryl, arylalkyl, heterocyclic-substituted loweralkyl or $-\text{C}(\text{O})\text{R}_{10}$ wherein R_{10} is loweralkyl, halo-substituted loweralkyl, $-\text{PO}_3\text{H}_2$ or $-\text{NR}_{11}\text{R}_{12}$ wherein R_{11} and R_{12} are independently selected from hydrogen and loweralkyl and
- (xiii) $-\text{NR}_{13}\text{R}_{14}$ or $-\text{CH}_2\text{NR}_{13}\text{R}_{14}$ wherein R_{13} and R_{14} are independently selected from (1) hydrogen, (2) lower alkyl, (3) arylalkyl, (4) $-\text{C}(\text{O})\text{R}_{15}$, (5) $-\text{S}(\text{O})_2\text{R}_{15}$ wherein R_{15} is loweralkyl or halo-substituted loweralkyl and (6) $-\text{R}_{16}-\text{R}_{17}$ wherein R_{16} is alkylene and R_{17} is
 - (a) $-\text{NR}_{18}\text{R}_{19}$ wherein R_{18} and R_{19} are independently selected from hydrogen and loweralkyl or
 - (b) unsubstituted or loweralkyl substituted aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyridinyl or pyrimidinyl, or R_{13} and R_{14} taken together with the nitrogen atom to which they are attached form a 5- to 7-membered aliphatic heterocycle and

R_4 is

- (i) hydrogen,
- (ii) loweralkyl,
- (iii) halo-substituted loweralkyl,
- (iv) $-\text{CN}$,
- (v) $-\text{NO}_2$,
- (vi) $-\text{NH}_2$,
- (vii) $-\text{NH}-\text{C}(=\text{N}(\text{R}_{25a}))(\text{R}_{26a})$ wherein R_{25a} is hydrogen, $-\text{CN}$ or $-\text{NO}_2$ and R_{26a} is hydrogen, loweralkyl, alkylamino, dialkylamino, alkoxy or thioalkoxy,
- (viii) $-\text{NH}(\text{R}_{26b})$ wherein R_{26b} is a 5-membered aromatic heterocyclic ring wherein the heterocyclic ring contains 1, 2, 3 or 4 nitrogen atoms

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- or 1 nitrogen atom and 1 oxygen atom or 2 nitrogen atoms and 1 oxygen atom or 1 oxygen atom and 1 sulfur atom and wherein the 5-membered heterocyclic ring is unsubstituted or substituted with a substituent selected from amino, alkylamino, dialkylamino, hydroxy, alkoxy, thioalkoxy, halo, loweralkyl and halo-substituted loweralkyl,
- (ix) -CHO or -CH(=N-OH),
- (x) tetrazolyl,
- (xi) -NHS(O)₂R₂₀ or -CH₂NHS(O)₂R₂₀ or -NHC(O)R₂₁ or -N(OH)C(O)R₂₁ or -CH₂NHC(O)R₂₁ or -CH₂N(OH)C(O)R₂₁ wherein R₂₀ is loweralkyl, halo-substituted loweralkyl or -NR_{27a}R_{27b} wherein R_{27a} and R_{27b} are independently selected from hydrogen, -OH and loweralkyl and R₂₁ is loweralkyl, halo-substituted loweralkyl, amino, alkylamino, dialkylamino or -COOH,
- (xii) -CH(OH)R₂₂ or -C(O)R₂₂ wherein R₂₂ is loweralkyl, halo-substituted loweralkyl, -CF₂COOR₂₃ or -CH₂COOR₂₃ wherein R₂₃ is hydrogen or a carboxy-protecting group,
- (xiii) -COOR₂₄ or -CH₂COOR₂₄ wherein R₂₄ is hydrogen or a carboxy-protecting group,
- (xiv) -C(O)NR₂₅R₂₆ or -CH₂C(O)NR₂₅R₂₆ or -NHC(O)NR₂₅R₂₆ or -CH₂NHC(O)NR₂₅R₂₆ or -NHC(S)NR₂₅R₂₆ or -CH₂NHC(S)NR₂₅R₂₆ wherein R₂₅ and R₂₆ are independently selected from hydrogen, loweralkyl, hydroxy, alkoxy, hydroxy-substituted loweralkyl, alkoxy-substituted loweralkyl, alkoxy-substituted alkoxy and -S(O)₂R_{28a} wherein R_{28a} is loweralkyl or aryl, or R₂₅ and R₂₆ taken together with the nitrogen atom to which they are attached form a 5- to 7- membered aliphatic heterocycle;
- (xv) -CH₂OR₂₇ wherein R₂₇ is selected from hydrogen, loweralkyl and -C(O)R₂₈ wherein R₂₈ is hydrogen, loweralkyl or aryl;
- (xvi) -CH₂NR₂₉R₃₀ wherein R₂₉ is selected from hydrogen, loweralkyl, -C(O)R₃₁, -C(O)NR₃₁R₃₂ and -S(O)₂R₃₃

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wherein R_{31} is selected from hydrogen, loweralkyl and aryl and R_{33} is selected from loweralkyl and halo-substituted loweralkyl and wherein R_{30} and R_{32} are independently selected from hydrogen, loweralkyl, hydroxy and alkoxy;

(xvii) $-\text{SO}_3\text{H}$, $-\text{OSO}_3\text{H}$ or $-\text{CH}_2\text{SO}_3\text{H}$,

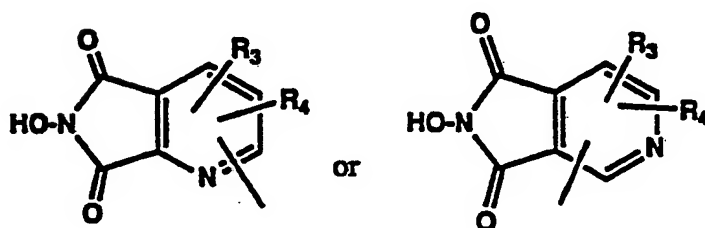
(xviii) $-\text{OPO}_3\text{H}$, $-\text{PO}_3\text{H}_2$ or $-\text{CH}_2\text{PO}_3\text{H}_2$,

(xix) $-\text{SO}_2\text{NR}_{25}\text{R}_{26}$ or $-\text{CH}_2\text{SO}_2\text{NR}_{25}\text{R}_{26}$ wherein R_{25} and R_{26} are defined as above and

(xx) $-\text{C}(\text{O})\text{NHSO}_2\text{R}_{59}$, $-\text{C}(\text{O})\text{NHC}(\text{O})\text{R}_{59}$ or $-\text{C}(\text{O})\text{NHNHSO}_2\text{R}_{59}$ wherein R_{59} is loweralkyl, halo-substituted loweralkyl or aryl;

or D is

(ii)



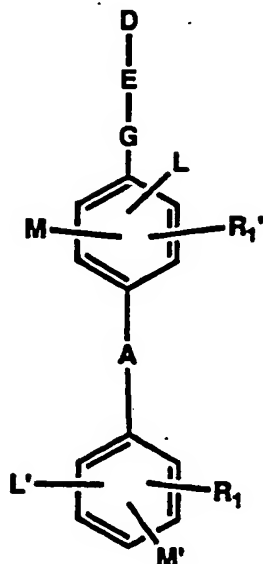
wherein R_3 and R_4 are defined as above;

or a pharmaceutically acceptable salt or prodrug thereof.

4. The compound of Claim 3 wherein A is a covalent bond, L, L', M, M' and R_1' are hydrogen, -G-E- is $-\text{CH}_2-\text{N}(\text{R}_5)-$ and D is a substituted purinyl group.

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5. A compound of the formula:



wherein

A is

- (i) a covalent bond,
- (ii) -O-,
- (iii) -C(O)-,
- (iv) -CH₂-,
- (v) -S-, -S(O)- or -S(O)₂-;

E-G is

- (i) -N(R₅)-,
- (ii) -O-,
- (iii) -S-,
- (iv) -N(R₅)-CH(R₅)-,
- (v) -O-CH(R₅)-,
- (vi) -S-CH(R₅)-,

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- (vii) $-C(R_5')(R_5)-CH(R_5)-$,
- (viii) $-CH(R_5)-C(R_5')(R_5)-$,
- (ix) $-CH(R_5)-N(R_5)-$,
- (x) $-CH(R_5)-O-$,
- (xi) $-CH(R_5)-S-$,
- (xii) $-N(R_5)-N(R_5)-$,
- (xiii) $-C(R_5)=C(R_5)-$ or
- (xiv) $-CH(R_5)-C(R_5')(R_5)-N(R_5)-$ wherein at each occurrence R_5 is independently selected from hydrogen, loweralkyl, alkoxy-substituted loweralkyl, halo-substituted loweralkyl, carboxy-substituted loweralkyl, heterocyclic-substituted loweralkyl, alkenyl, alkynyl, cycloalkyl or cycloalkylalkyl and R_5' is hydrogen, halo, hydroxy, carboxy, alkoxy or thioalkoxy;

L, L', M and M' are independently selected from

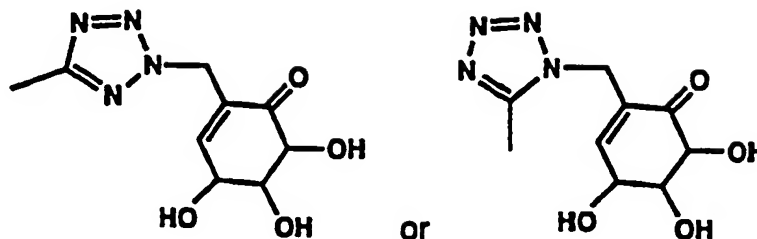
- (i) hydrogen,
- (ii) loweralkyl,
- (iii) halo-substituted loweralkyl,
- (iv) halo,
- (v) $-CN$,
- (vi) $-NO_2$,
- (vii) $-OH$,
- (viii) hydroxy-substituted loweralkyl,
- (ix) alkoxy-substituted loweralkyl,
- (x) $-NH_2$,
- (xi) alkylamino,
- (xii) dialkylamino,
- (xiii) $-SH$,
- (xiv) alkoxy and
- (xv) thioalkoxy;

R_1 and R_1' are independently selected from

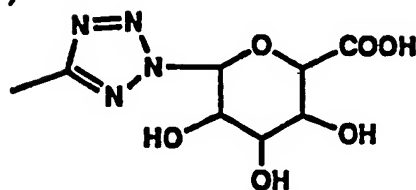
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(i) tetrazolyl,

(ii)



(iii)



(iv) $\text{-NH-C(=N(R}_{50\text{a}}))\text{(R}_{51\text{a}})$ wherein $\text{R}_{50\text{a}}$ is hydrogen, -CN or -NO_2 and $\text{R}_{51\text{a}}$ is hydrogen, loweralkyl, alkylamino, dialkylamino, alkoxy or thioalkoxy,

(v) $\text{-NH(R}_{51\text{b}})$ wherein $\text{R}_{51\text{b}}$ is a 5-membered aromatic heterocyclic ring wherein the heterocyclic ring contains 1, 2, 3 or 4 nitrogen atoms or 1 nitrogen atom and 1 oxygen atom or 2 nitrogen atoms and 1 oxygen atom or 1 oxygen atom and 1 sulfur atom and wherein the 5-membered heterocyclic ring is unsubstituted or substituted with a substituent selected from amino, alkylamino, dialkylamino, hydroxy, alkoxy, thioalkoxy, halo, loweralkyl and halo-substituted loweralkyl,

(vi) -COOR_6 or $\text{-CH}_2\text{COOR}_6$ wherein R_6 is hydrogen or a carboxy-protecting group or

(vii) $\text{-NHS(O)}_2\text{R}_7$ or $\text{-CH}_2\text{NHS(O)}_2\text{R}_7$ or $\text{-NHC(O)R}_{7\text{a}}$ or $\text{-CH}_2\text{NHC(O)R}_{7\text{a}}$ wherein R_7 is loweralkyl, halo-substituted loweralkyl or $\text{-NR}_{7\text{b}}\text{R}_{7\text{c}}$ wherein $\text{R}_{7\text{b}}$ and $\text{R}_{7\text{c}}$ are independently selected from hydrogen and loweralkyl and $\text{R}_{7\text{a}}$ is loweralkyl, halo-substituted loweralkyl, amino, alkylamino, dialkylamino or -COOH ;

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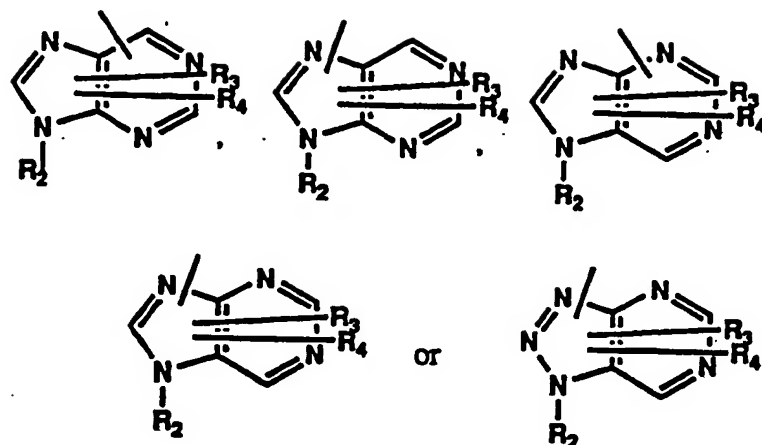
- (viii) $-\text{C}(\text{O})\text{NR}_{50}\text{R}_{51}$ or $-\text{CH}_2\text{C}(\text{O})\text{NR}_{50}\text{R}_{51}$ or $-\text{NHC}(\text{O})\text{NR}_{50}\text{R}_{51}$ or $-\text{CH}_2\text{NHC}(\text{O})\text{NR}_{50}\text{R}_{51}$ or $-\text{NHC}(\text{S})\text{NR}_{50}\text{R}_{51}$ or $-\text{CH}_2\text{NHC}(\text{S})\text{NR}_{50}\text{R}_{51}$ wherein R_{50} and R_{51} are independently selected from hydrogen, loweralkyl, hydroxy, alkoxy, hydroxy-substituted loweralkyl, alkoxy-substituted loweralkyl, alkoxy-substituted alkoxy and $-\text{S}(\text{O})_2\text{R}_{50a}$ wherein R_{50a} is loweralkyl or aryl, or R_{50} and R_{51} taken together with the nitrogen atom to which they are attached form a 5- to 7-membered aliphatic heterocycle;
- (ix) $-\text{CH}_2\text{OR}_{52}$ wherein R_{52} is selected from hydrogen, loweralkyl and $-\text{C}(\text{O})\text{R}_{53}$ wherein R_{53} is hydrogen, loweralkyl or aryl;
- (x) $-\text{CH}(\text{OH})\text{R}_{52a}$ or $-\text{C}(\text{O})\text{R}_{52a}$ wherein R_{52a} is loweralkyl, halo-substituted loweralkyl, $-\text{CF}_2\text{COOR}_{53a}$ or $-\text{CH}_2\text{COOR}_{53a}$ wherein R_{53a} is hydrogen or a carboxy-protecting group,
- (xii) $-\text{CH}_2\text{NR}_{54}\text{R}_{55}$ wherein R_{54} is selected from hydrogen, loweralkyl, $-\text{C}(\text{O})\text{R}_{56}$, $-\text{C}(\text{O})\text{NR}_{56}\text{R}_{57}$ and $-\text{S}(\text{O})_2\text{R}_{58}$ wherein R_{56} is selected from hydrogen, loweralkyl and aryl and R_{58} is selected from lower alkyl and halo-substituted loweralkyl and wherein R_{55} and R_{57} are independently selected from hydrogen, loweralkyl, hydroxy and alkoxy;
- (xiii) $-\text{SO}_3\text{H}$, $-\text{OSO}_3\text{H}$ or $-\text{CH}_2\text{SO}_3\text{H}$,
- (xiv) $-\text{OPO}_3\text{H}_2$, $-\text{PO}_3\text{H}_2$ or $-\text{CH}_2\text{PO}_3\text{H}_2$,
- (xv) $-\text{SO}_2\text{NR}_{50}\text{R}_{51}$ or $-\text{CH}_2\text{SO}_2\text{NR}_{50}\text{R}_{51}$ wherein R_{50} and R_{51} are defined as above and
- (xvi) $-\text{C}(\text{O})\text{NHSO}_2\text{R}_{60}$, $-\text{C}(\text{O})\text{NHC}(\text{O})\text{R}_{60}$ or $-\text{C}(\text{O})\text{NHNHSO}_2\text{R}_{60}$ wherein R_{60} is loweralkyl, halo-substituted loweralkyl or aryl;

with the proviso that one of R_1 and R_1' is hydrogen, but R_1 and R_1' are not both hydrogen;

and

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D is



wherein R₂ is selected from hydrogen, loweralkyl, carboxy-substituted loweralkyl or alkoxycarbonyl-substituted loweralkyl,

R₃ is

- (i) hydrogen,
- (ii) loweralkyl,
- (iii) halo,
- (iv) halo-substituted loweralkyl,
- (v) thioalkoxy,
- (vi) alkoxy-substituted loweralkyl,
- (vii) thioalkoxy-substituted loweralkyl,
- (viii) aryl,
- (ix) arylalkyl,
- (x) -NO₂,
- (xi) -COOR₈ wherein R₈ is hydrogen or a carboxy-protecting group,
- (xii) -OR₉ wherein R₉ is hydrogen, loweralkyl, halo-substituted loweralkyl, aryl, arylalkyl, heterocyclic-substituted loweralkyl or -C(O)R₁₀ wherein R₁₀ is loweralkyl, halo-substituted loweralkyl, -PO₃H₂ or -NR₁₁R₁₂ wherein R₁₁ and R₁₂ are independently selected from hydrogen and loweralkyl and

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- (xiii) $\text{-NR}_{13}\text{R}_{14}$ or $\text{-CH}_2\text{NR}_{13}\text{R}_{14}$ wherein R_{13} and R_{14} are independently selected from (1) hydrogen, (2) lower alkyl, (3) arylalkyl, (4) -C(O)R_{15} , (5) $\text{-S(O)}_2\text{R}_{15}$ wherein R_{15} is loweralkyl or halo-substituted loweralkyl and
- (6) $\text{-R}_{16}\text{-R}_{17}$ wherein R_{16} is alkylene and R_{17} is
- (a) $\text{-NR}_{18}\text{R}_{19}$ wherein R_{18} and R_{19} are independently selected from hydrogen and loweralkyl or
- (b) unsubstituted or loweralkyl substituted aziridiny, azetidiny, pyrrolidiny, piperidiny, piperaziny, morpholiny, thiomorpholiny, pyridiny or pyrimidiny, or R_{13} and R_{14} taken together with the nitrogen atom to which they are attached form a 5- to 7-membered aliphatic heterocycle and

R_4 is

- (i) hydrogen,
- (ii) loweralkyl,
- (iii) halo-substituted loweralkyl,
- (iv) -CN ,
- (v) -NO_2 ,
- (vi) -NH_2 ,
- (vii) $\text{-NH-C(=N(R}_{25a}))\text{(R}_{26a})$ wherein R_{25a} is hydrogen, -CN or -NO_2 and R_{26a} is hydrogen, loweralkyl, alkylamino, dialkylamino, alkoxy or thioalkoxy,
- (viii) $\text{-NH(R}_{26b})$ wherein R_{26b} is a 5-membered aromatic heterocyclic ring wherein the heterocyclic ring contains 1, 2, 3 or 4 nitrogen atoms or 1 nitrogen atom and 1 oxygen atom or 2 nitrogen atoms and 1 oxygen atom or 1 oxygen atom and 1 sulfur atom and wherein the 5-membered heterocyclic ring is unsubstituted or substituted with a substituent selected from amino, alkylamino, dialkylamino, hydroxy, alkoxy, thioalkoxy, halo, loweralkyl and halo-substituted loweralkyl,
- (ix) -CHO or -CH(=N-OH) ,

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- (x) tetrazolyl,
- (xi) $-\text{NHS}(\text{O})_2\text{R}_{20}$ or $-\text{CH}_2\text{NHS}(\text{O})_2\text{R}_{20}$ or $-\text{NHC}(\text{O})\text{R}_{21}$ or $-\text{N}(\text{OH})\text{C}(\text{O})\text{R}_{21}$ or $-\text{CH}_2\text{NHC}(\text{O})\text{R}_{21}$ or $-\text{CH}_2\text{N}(\text{OH})\text{C}(\text{O})\text{R}_{21}$ wherein R_{20} is loweralkyl, halo-substituted loweralkyl or $-\text{NR}_{27a}\text{R}_{27b}$ wherein R_{27a} and R_{27b} are independently selected from hydrogen, $-\text{OH}$ and loweralkyl and R_{21} is loweralkyl, halo-substituted loweralkyl, amino, alkylamino, dialkylamino or $-\text{COOH}$,
- (xii) $-\text{CH}(\text{OH})\text{R}_{22}$ or $-\text{C}(\text{O})\text{R}_{22}$ wherein R_{22} is loweralkyl, halo-substituted loweralkyl, $-\text{CF}_2\text{COOR}_{23}$ or $-\text{CH}_2\text{COOR}_{23}$ wherein R_{23} is hydrogen or a carboxy-protecting group,
- (xiii) $-\text{COOR}_{24}$ or $-\text{CH}_2\text{COOR}_{24}$ wherein R_{24} is hydrogen or a carboxy-protecting group,
- (xiv) $-\text{C}(\text{O})\text{NR}_{25}\text{R}_{26}$ or $-\text{CH}_2\text{C}(\text{O})\text{NR}_{25}\text{R}_{26}$ or $-\text{NHC}(\text{O})\text{NR}_{25}\text{R}_{26}$ or $-\text{CH}_2\text{NHC}(\text{O})\text{NR}_{25}\text{R}_{26}$ or $-\text{NHC}(\text{S})\text{NR}_{25}\text{R}_{26}$ or $-\text{CH}_2\text{NHC}(\text{S})\text{NR}_{25}\text{R}_{26}$ wherein R_{25} and R_{26} are independently selected from hydrogen, loweralkyl, hydroxy, alkoxy, hydroxy-substituted loweralkyl, alkoxy-substituted loweralkyl, alkoxy-substituted alkoxy and $-\text{S}(\text{O})_2\text{R}_{28a}$ wherein R_{28a} is loweralkyl or aryl, or R_{25} and R_{26} taken together with the nitrogen atom to which they are attached form a 5- to 7- membered aliphatic heterocycle;
- (xv) $-\text{CH}_2\text{OR}_{27}$ wherein R_{27} is selected from hydrogen, loweralkyl and $-\text{C}(\text{O})\text{R}_{28}$ wherein R_{28} is hydrogen, loweralkyl or aryl;
- (xvi) $-\text{CH}_2\text{NR}_{29}\text{R}_{30}$ wherein R_{29} is selected from hydrogen, loweralkyl, $-\text{C}(\text{O})\text{R}_{31}$, $-\text{C}(\text{O})\text{NR}_{31}\text{R}_{32}$ and $-\text{S}(\text{O})_2\text{R}_{33}$ wherein R_{31} is selected from hydrogen, loweralkyl and aryl and R_{33} is selected from loweralkyl and halo-substituted loweralkyl and wherein R_{30} and R_{32} are independently selected from hydrogen, loweralkyl, hydroxy and alkoxy;
- (xvii) $-\text{SO}_3\text{H}$, $-\text{OSO}_3\text{H}$ or $-\text{CH}_2\text{SO}_3\text{H}$,

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(xviii) $-\text{OPO}_3\text{H}$, $-\text{PO}_3\text{H}_2$ or $-\text{CH}_2\text{PO}_3\text{H}_2$,

(xix) $-\text{SO}_2\text{NR}_{25}\text{R}_{26}$ or $-\text{CH}_2\text{SO}_2\text{NR}_{25}\text{R}_{26}$ wherein R_{25} and R_{26} are defined as above and

(xx) $-\text{C}(\text{O})\text{NHSO}_2\text{R}_{59}$, $-\text{C}(\text{O})\text{NHC}(\text{O})\text{R}_{59}$ or $-\text{C}(\text{O})\text{NHNHSO}_2\text{R}_{59}$ wherein R_{59} is loweralkyl, halo-substituted loweralkyl or aryl;

or a pharmaceutically acceptable salt or prodrug thereof.

6. The compound of Claim 5 wherein A is a covalent bond, L, L', M, M' and $\text{R}_{1'}$ are hydrogen and -G-E- is $-\text{CH}_2-\text{N}(\text{R}_5)-$.

7. A pharmaceutical composition for blocking the interaction of angiotensin II with angiotensin II receptors comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Claim 1.

8. A pharmaceutical composition for treating hypertension or congestive heart failure comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Claim 1.

9. A method of blocking the interaction of angiotensin II with angiotensin II receptors comprising administering to a human or other mammal in need a therapeutically effective amount of a compound of Claim 1.

10. A method of treating hypertension or heart failure comprising administering to a human or other mammal in need a therapeutically effective amount of a compound of Claim 1.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/01105

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. :

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CHEMICAL ABSTRACTS**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| X,P | US,A, 5,102,880 (CHAKRAVARTY ET AL) 07 APRIL 1992 See entire document | 1-10 |
| X,P | US,A, 5,124,335 (PATCHETT ET AL) 23 JUNE 1992 See entire document | 1-10 |
| X | UK, A, 2,239,240 (SANTILLI ET AL) 26 JUNE 1991 See entire document | 1-10 |
| X | EP,A, 0,415,886 (HEROLD ET AL) 06 MARCH 1991 See entire document | 1-10 |

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

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|---|--|
| Special categories of cited documents: | |
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| *E* earlier document published on or after the international filing date | *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
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| *O* document referring to an oral disclosure, use, exhibition or other means | *A* document member of the same patent family |
| *P* document published prior to the international filing date but later than the priority date claimed | |

Date of the actual completion of the international search

21 APRIL 1993

Date of mailing of the international search report

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Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Authorized officer

FLOYD D. HIGEL
YEN NGOC-HO
INTERNATIONAL DIVISION
Telephone N. (703) 308-1235

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/01105

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| X | EP,A, 0,430,300 (MORIMOTO ET AL) 05 JUNE 1991 See entire document | 1-10 |
| X | WO,A, 91/19715 (BOVY ET AL) 26 DECEMBER 1991 See entire document | 1-10 |

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (5):

C07D 471/04; C07D 487/04; C07D 473/00; A61K 31/435, 31/495, 31/52, 31/53, 31/44

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/81, 212, 234, 2, 235, 243, 300; 544/58.4, 112/127, 184, 236, 246, 256, 262, 264, 267, 275, 277; 546/23, 113, 114, 115, 183; 540/599